ALKALOIDS OF ARISTOTELIA SPECIES

by

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Submitted in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF TASMANIA
HOBART

NOVEMBER, 1981

"To my parents"

Except as stated therein this thesis contains no material which has been accepted for the award of any other degree or diploma in any university, and, to the best of my knowledge and belief, this thesis contains no copy or paraphrase of material previously published or written by another person, except when due reference is made in the text of this thesis.

CONTENTS

ACKNOWLEDGEMENTS

I wish to express my appreciation and gratitude for the invaluable supervision, guidance and continuous encouragement given by Dr. I.R.C. Bick throughout the course of this study.

I wish to acknowledge the helpful advice given by Dr. J.B. Bremner and my colleagues.

Thanks are due to Professor A.H. White (The University of Western Australia) for X-ray crystallographic studies, and to Professor M. Hesse (The University of Zürich) for a gift of two samples. I am also grateful to Dr. A.J. Jones (The National N.M.R. Centre, Canberra) and Mr. R. Thomas for the measurement of P.M.R. and ^{13}C N.M.R. spectra, and to Mr. J. Bignall, Mr. N.W. Davies and Mr. M. Power of the Central Science Laboratory of this University, and to Mr. C. MacDonald (C.S.I.R.O., Canberra) for assistance in determining mass spectra.

I am especially grateful to Mrs. H. Hen for assistance in the preparation of the diagrams, and to Mrs. B. Thomson for typing this thesis.

The award of a Commonwealth Scholarship by the Australian Development Assistance Bureau is gratefully acknowledged.

Finally, I would like to thank my wife, Fatema, and two sons, Tariq and Arif, for their tolerance during the period this work was undertaken.

ABSTRACT

A detailed phytochemical examination of the alkaloid content of two species of the family Elaeocarpaceae - *Aristotelia serrata* W.R.B. Oliver and *Aristotelia fruticosa* Hook F. - has been undertaken.

A new group of indole alkaloids has been isolated from the abovementioned species. Of the sixteen bases obtained, one had been described previously and was reisolated from *Aristotelia serrata*. Spectroscopic and chemical evidence for the structures of the fifteen new minor alkaloids are presented. X-ray crystallographic studies confirmed the structures of two of them, and established the relative stereochemistries. In one case, the structural assignment was confirmed by synthesis. The absolute stereochemistries of altogether six alkaloids have been established through chemical correlations.

A possible biosynthetic scheme for the *Aristotelia* alkaloids is presented.

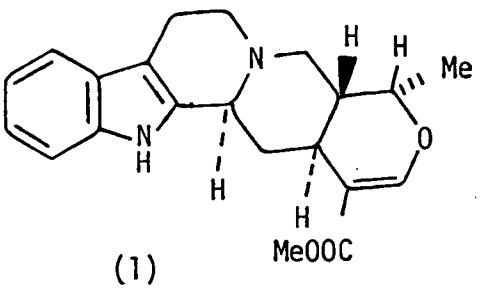
A preliminary investigation of one species of the family Menispermaceae - *Pachygone vieillardii* - has been made, and the results appear in Appendix-1. Of the five alkaloids isolated from this species, one appears to have a bisbenzylisoquinoline type of structure. Tentative evidence is presented to support a proaporphine-type structure for two further alkaloids, and a morphinane-type structure for each of the remaining pair of alkaloids.

CHAPTER 1

General Introduction

1.A.1. Monoterpenoid Indole Alkaloids

The indole alkaloids form a very large class containing well over 1400 alkaloids. The comprehensive volume of Boit[1], and the tables of Willaman and Schubert[2], Hesse[3], and Holubek and Štrouf[4] illustrate their structural variations and distribution in plant families. Snieckus[5] has made a compilation of plant species which he has classified according to the structural types of indole alkaloid they contain. His table also incorporates a major division into simple and complex indole alkaloids. In the case of a simple indole alkaloid, the main distinguishable feature in its structure is the presence of a tryptamine unit, which may appear in a slightly modified form (e.g. by oxidation or methylation), as a cyclised structure or a dimeric variation thereof, or as a modification which incorporates a short chain (e.g. C_4, C_2 ...). On the other hand, a complex indole alkaloid has a terpenoid unit joined to a tryptamine moiety which is usually unmodified and easily recognised. The terpenoid unit almost always comprises a C-10 or C-9 residue, and when joined to the tryptamine moiety forms an alkaloid of the monoterpenoid indole group. This type, with many variations, accounts for an overwhelming majority of indole alkaloids. Despite their bewildering variety, three main classes of indole alkaloid have been recognised: (a) the *Corynanthe-Strychnos* type, e.g. ajmalicine (1) and akuammicine (2) which possess the terpenoid unit (3); (b) the *Aspidosperma* type, e.g. vindoline (4), in which the terpenoid



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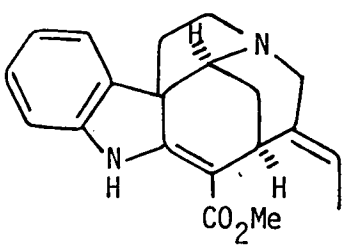

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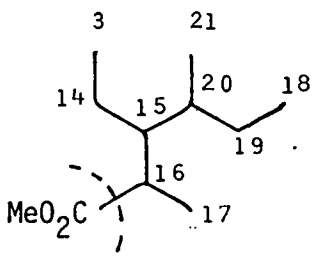
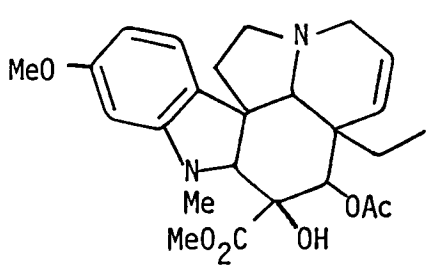


(3)

unit appears as (5); and (c) the *Iboga* type, e.g. catharanthine (6), which has a different arrangement again (7) of the terpenoid unit. The C-9 moiety is invariably formed through loss of the ester carbon (shown by dotted lines).



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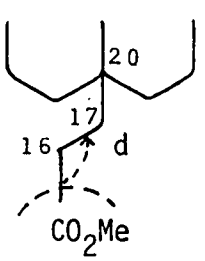

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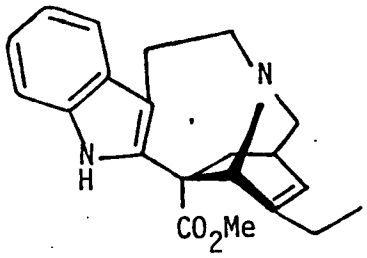

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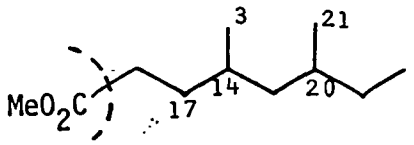

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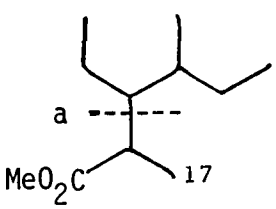
According to Schmid[6], there are two more main classes of monoterpenoid indole alkaloids: the *Secodine* type formed by the cleavage (a) in (8) and attachment of the three carbon unit to the 2-position of the indole nucleus, to form the basic skeleton (9) of this class of alkaloid, e.g. secodine (10).



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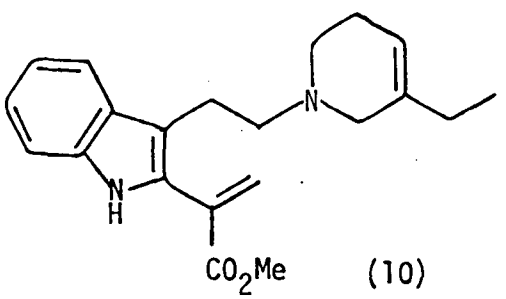

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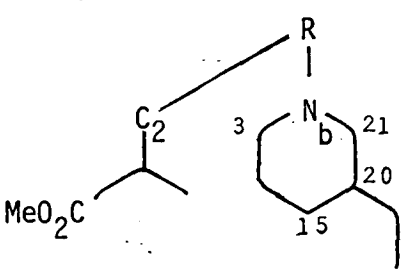

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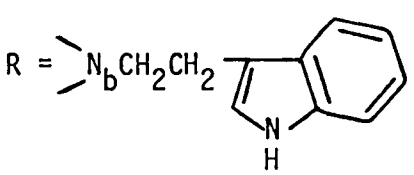
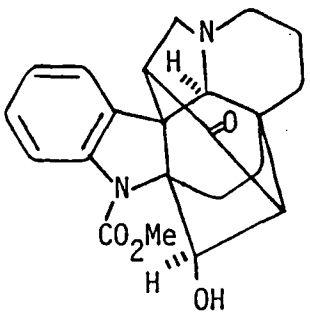


Rearrangement of d in (5) leads to the structural unit (11), from which class 5 (*Fruticosine* type) alkaloids are derived, e.g. fruticosine (12).



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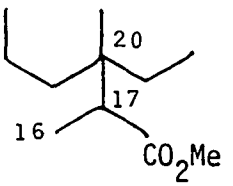


(11)

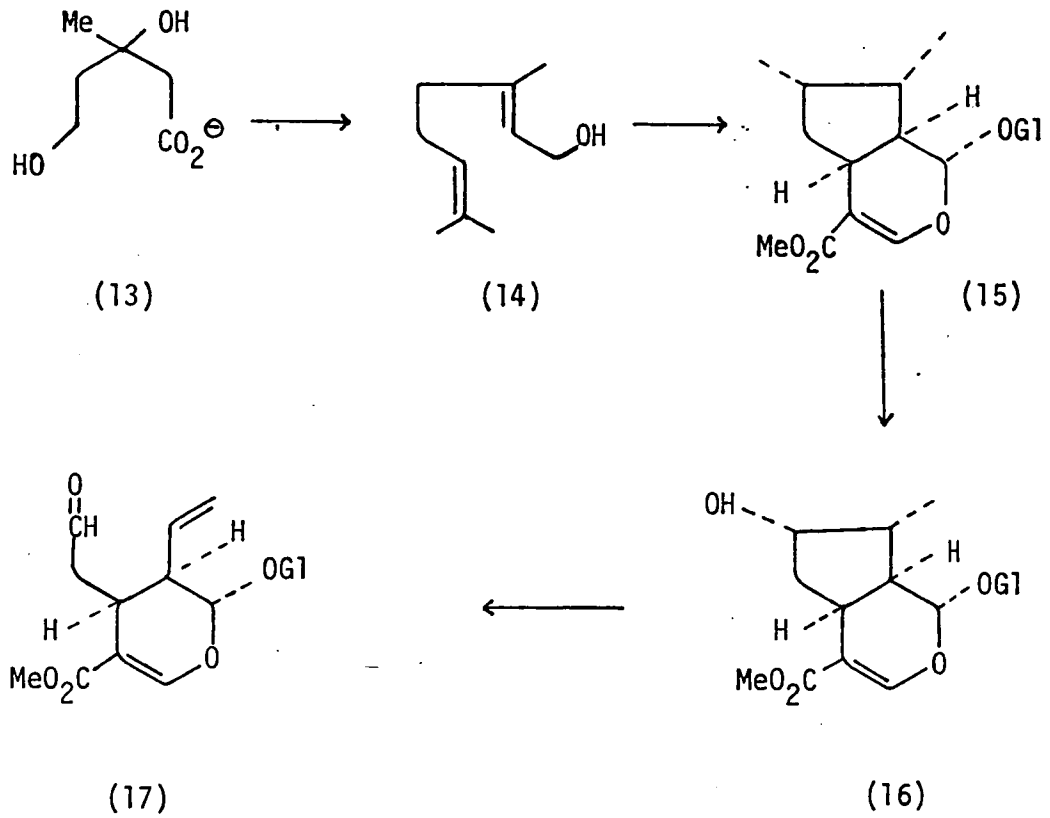
The different alkaloids comprising each of these classes then arise by minor skeletal variations within each type.

1.A.2. Biosynthesis

The biosynthesis of indole alkaloids has been well reviewed by a number of authors.[6-11] Although the complete biogenetic pathway to each individual alkaloid has not been established, the origin of the aromatic portion as well as the terpenoid unit, their combination to form a common precursor, and the subsequent transformation of the latter into some of the main groups of indole alkaloids are now known. The two nitrogens and the aromatic portion are derived from tryptophan via its decarboxylation product, tryptamine. The nine- or ten-carbon moiety is terpenoid in nature, and has been shown to originate from two moles of mevalonate (13) by way of geraniol (14) → deoxyloganin (15) → loganin (16) → secologanin (17) (Scheme 1).

A Mannich-type reaction between tryptamine (18) and secologanin (17)

Scheme 1

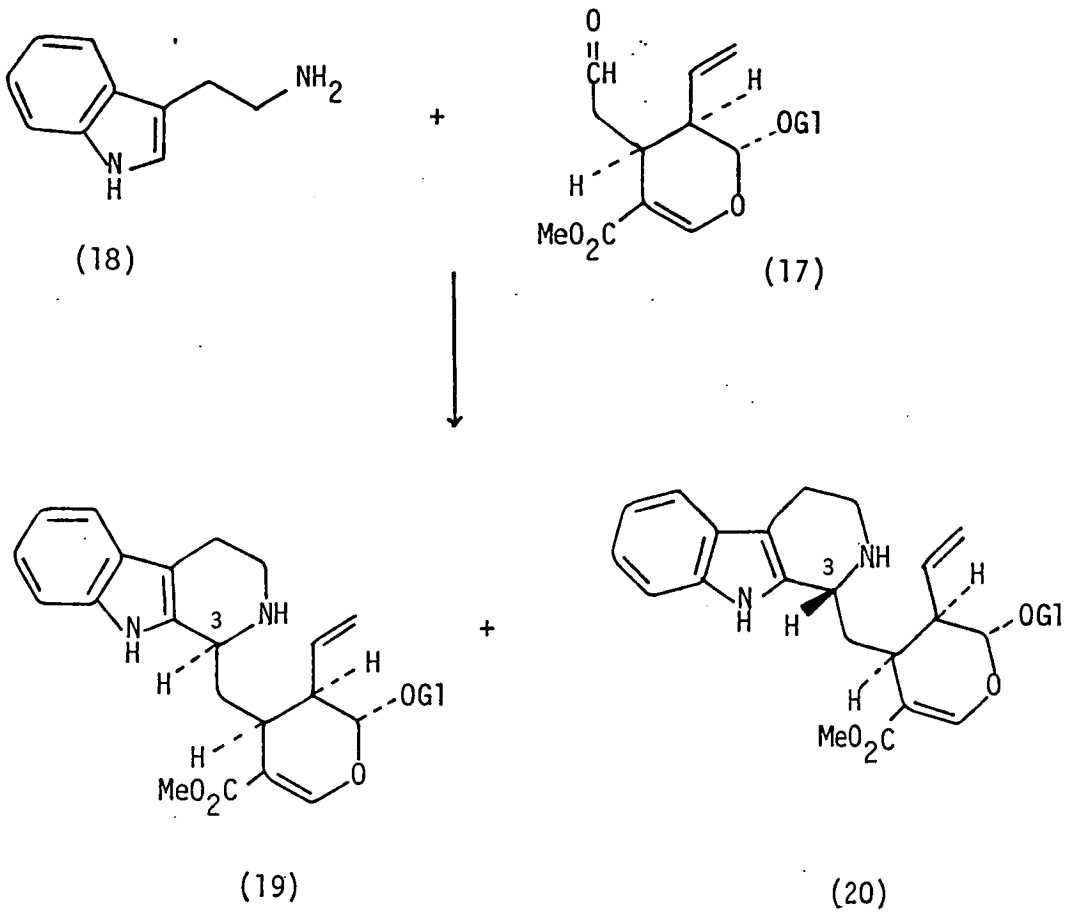


(13) (14) (15)

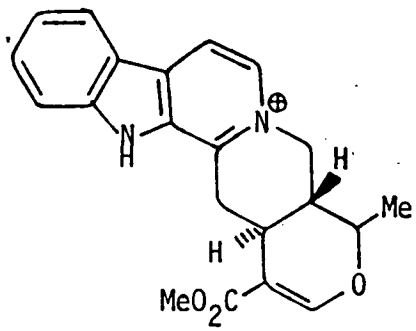
(17) (16)

affords vincoside (20) and strictosidine (19) (Scheme 2), which are epimeric at C-3. The monoterpene indole alkaloids of the *Corynanthe* type (e.g. ajmalicine (1)); *Aspidosperma*, (vindoline (4)); and *Iboga* (catharanthine (6)) were considered to be derived from vincoside (20) which has the (R) configuration at C-3 (3β-H). Because most of these alkaloids have 3α-H at C-3, an unexpected inversion would have to be postulated. According to a recent review[11], however, using a cell-free enzyme preparation isolated from *Catharanthus roseus* cell suspension cultures,[12-14] it has now been shown that the sole product of the reaction between tryptamine (18) and secologanin (17) *in vivo* is strictosidine (19), the epimer of vincoside with the (3S)-3α-H configuration. Cell-free preparations of cell-suspension cultures of *Amsonia tabernaemontana*, *Rhazya orientalis* and *Vinca minor* have

Scheme 2



also been observed to convert tryptamine and secologonin into strictosidine; the formation of vincoside has never been observed.[12a] That strictosidine is the correct alkaloid precursor has been confirmed for whole-plant biosynthesis.[12a] Doubly labelled strictosidine has also been shown to be incorporated in the case of *C. roseus* into representatives of the three main groups of alkaloids, e.g. ajmalicine (1), serpentine (21), vindoline (4) and catharanthine (6). Further results[15,16] demonstrate the universal intermediacy of strictosidine (19) in the biosynthesis of terpenoid indole alkaloids with the 3α- configuration and also those with the 3β- arrangement in taxonomically very different families.



(21)

The transformation of strictosidine (19) into alkaloids of the main groups has been shown to follow the sequence: *Coryanthe-Strychnos* —— *Aspidosperma* —— *Iboga*, according to sequential isolation work done on *C. roseus*[17] and *Stemmadenia pubescens*. Several reviews[6,8-11,18] have summarised the biogenetic pathway to the formation of certain alkaloids of these main groups, and some others as well.

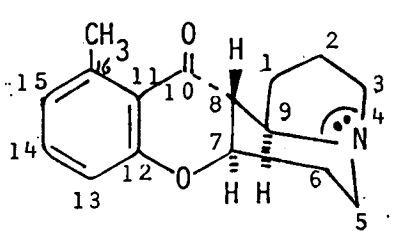
1.B. The Alkaloids of the Elaeocarpaceae

1.B.1. Elaeocarpus Alkaloids

The Elaeocarpaceae[19] are a small family containing over 350 species in seven genera. Of these only eight *Elaeocarpus*,[20,21] one *Peripentadenia*,[22] one *Aceratium*[23] and four *Aristotelia* species have so far been shown to contain alkaloids.

The literature on the chemistry of *Elaeocarpus* alkaloids has been reviewed by Saxton,[24] and Johns and Lamberton.[25] A new family of indolizidine alkaloids has been isolated[25,26,50] from one Indian and six New Guinea species. The only indole alkaloid, elaeocarpidine (41), occurs in the two New Guinea species *E. densiflorus* Knuth. and *E. dolichostylis* Schltr.. The botanical distribution of the *Elaeocarpus* alkaloids in different species is shown in Table 1.[25]

The two C^{16} aromatic alkaloids (±)-elaeocarpine (22) and (±)-isoelaeocarpine (23) occur in nature virtually as racemic forms. The complete stereochemistry of (±)-elaeocarpine hydrobromide was established by X-ray crystal structural analysis[27,28] and the structure of (±)-isoelaeocarpine was established by a detailed comparison of the ^1H nmr spectra of (22) and (23).[27,29] They have been synthesized by four independent groups: Tanaka and Iijima,[38] Onaka,[39] Howard,[51,52] and by Tufariello.[53]



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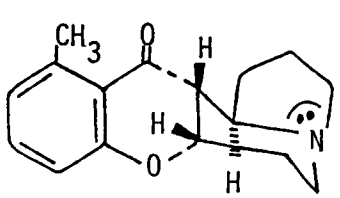


(23)

Table 1

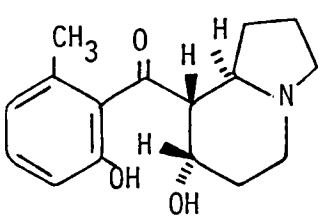
Botanical Distribution

Plant	Alkaloid	Refs.
E. altisectus Schltr.	(-)-Isoelaeocarpiline	30
E. densiflorus Knuth	Elaeocarpidine	36,37
E. dolichostylis Schltr.	Elaeocarpidine	32
	(+)-Elaeocarpiline	31,32
	Elaeocarpine	32
	(-)-Isoelaeocarpiline	31,32
	Isoelaeocarpine	32
E. ganitrus Roxb.	(±)-Elaeocarpine	26
	(±)-Isoelaeocarpine	26
	Rudrakine	50
E. kaniensis Schltr.	Elaeokanidine A	34,35
	Elaeokanidine B	34,35
	Elaeokanidine C	34,35
	Elaeokanine A	34,35
	Elaeokanine B	34,35
	Elaeokanine C	34,35
	Elaeokanine D	34,35
	Elaeokanine E	34,35
E. polydactylus Schltr.	Elaeocarpidine	29
	(±)-Elaeocarpine	27,28,29
	(+)-Isoelaeocarpicine	29,31
	(±)-Isoelaeocarpine	27,29
E. sphaericus (Gaertn.) K. Schum.	(-)-Alloelaeocarpiline	39,33
	Elaeocarpidine	30
	(+)-Elaeocarpiline	30,33

Table 1 continued

E. sphaericus (Gaertn.) K. Schum.	(±)-Elaeocarpine	30
	(+)-Epialloelaeocarpiline	30,33
	(-)-Epielaeocarpiline	30,33
	(+)-Epi-isoelaeocarpiline	30,33
	(-)-Isoelaeocarpiline	30,33
	(±)-Isoelaeocarpine	30
	(+)-Pseudoepi-isoelaeocarpiline	30,33
	Unidentified base, $C_{16}H_{24}N_2O_2$	30

The only phenolic alkaloid, (+)-isoelaeocarpicine, was assigned the structure (24). The relative stereochemistry of this alkaloid was shown to resemble that of (±)-isoelaeocarpine by analysis of the PMR spectra. It has been synthesised by Tufariello.[53]



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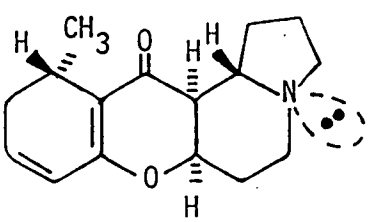
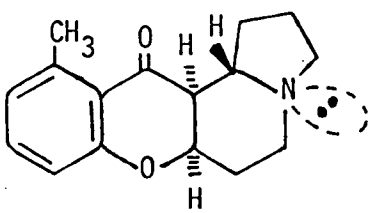


(25)

The structures and absolute stereochemistry of the seven isomeric dienone alkaloids have been determined by PMR spectral studies, and by their conversion into known compounds. The absolute configuration at C-16 in each case is the same; it has been established by the isolation of S-(-)-methylsuccinic acid from the products of oxidation of (-)-isoelaeocarpiline (25) with potassium permanganate. The absolute configurations of (-)-isoelaeocarpiline (25) and (+)-epi-

isoelaeocarpiline (27) were determined by their conversion into (-)-isoelaeocarpine (26) and (+)-isoelaeocarpine (the optical enantiomer of (26)) respectively when heated with palladium-charcoal in benzene. Similarly (+)-elaeocarpiline (28) was aromatized into (+)-elaeocarpine (29), and (-)-epi-elaeocarpiline (30) into (-)-elaeocarpine (the optical enantiomer of (29)).



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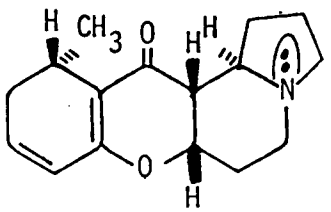

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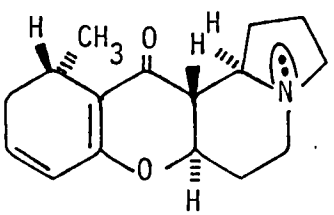

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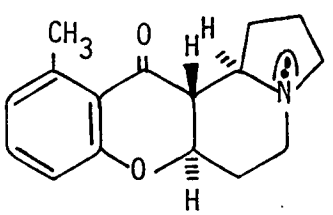
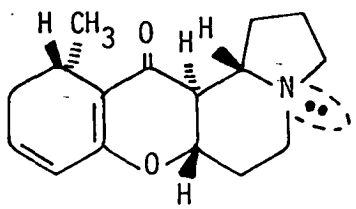


(29)

Their structures and absolute configurations have been shown to be (28) and (30) respectively. The instability of (+)-epialloelaeocarpiline when absorbed on thin-layer plates of Kieselgel G, and its consequent conversion into (+)-epi-isoelaeocarpiline (27) resulted in the formation of (+)-isoelaeocarpine (23) on heating with palladium-charcoal in benzene. The presence of a *trans*-diaxial conformation for C_7-H, C_8-H in the PMR spectrum of (+)-epi-elaeocarpiline thus showed its structure to be (31), the C-8 epimer of (+)-epi-isoelaeocarpiline (27). Like (+)-epi-alloelaeocarpiline,

(-)-alloelaeocarpiline is also unstable and is easily converted into (-)-isoelaeocarpiline (25) presumably by a similar epimerization at the C-8 centre. (-)-Alloelaeocarpiline (32) has therefore been formulated as the C-8 epimer of (-)-isoelaeocarpiline (25).



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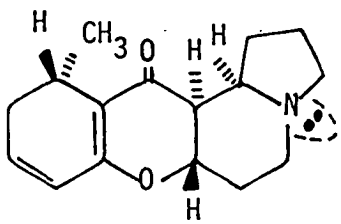

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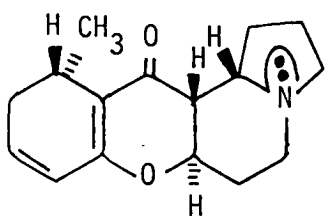

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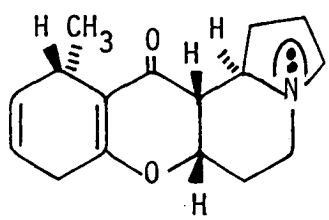
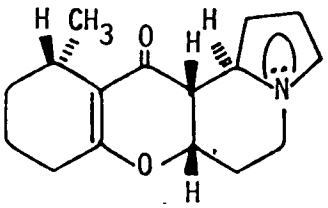


(33)

Pseudoepi-isoelaeocarpiline, isomeric with the other conjugated dienone alkaloids, has been shown to have the absolute configuration (33) as a result of its conversion on catalytic hydrogenation into (+)-dihydroepi-isoelaeocarpiline (34). The latter was obtained as one of the products when (+)-epi-isoelaeocarpiline was heated with palladium-charcoal in benzene.

E. kaniensis is quite different in having several alkaloids with a C^{12} skeleton. They have been divided into two groups - the elaeokanines and elaeokanidines with one and two nitrogen atoms respectively.



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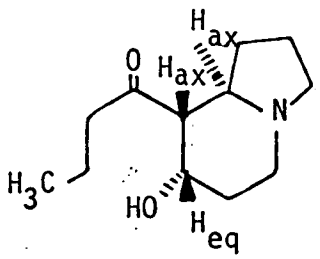
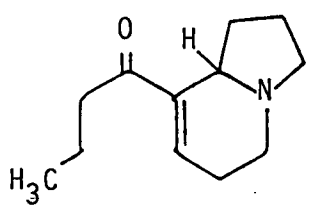


(35)

The structure and stereochemistry of elaeokanine C (35) was determined by PMR spectral studies, and proof of the structure was obtained by several syntheses[35,52,54,56] of the racemic form. Elaeokanine A was shown to have the structure (36) and proved to be spectroscopically identical with the dehydration product of elaeokanine C. Racemic elaeokanine A was synthesised by three independent groups: Howard,[52] Tufariello[54] and by Watanabe.[56]



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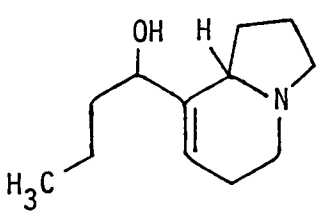
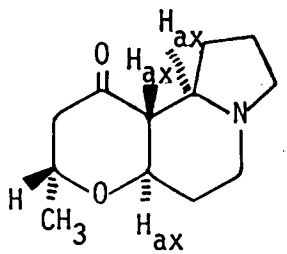


(37)

The molecular formula of elaeokanine B showed two additional hydrogen atoms as compared to elaeokanine A, and its infrared spectrum indicated the presence of an alcohol group. The relationship of elaeokanine B to elaeokanine A was established by the identification of elaeokanine B (37) as the $NaBH_4$- reduction product of elaeokanine A (36). Howard[52] and Watanabe[56] reported the synthesis of (±)-elaeokanine B. The similarity of their mass spectra to those of other Elaeocarpus alkaloids and a study of their PMR spectra led to the structures (38) and (39), respectively, for the two isomeric alkaloids elaeokanine D and elaeokanine E. Racemic elaeokanine E was later synthesised by Watanabe.[57]



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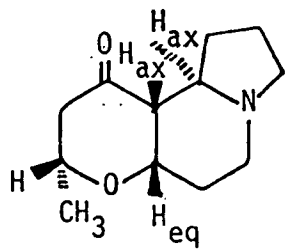
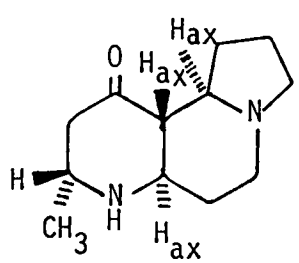
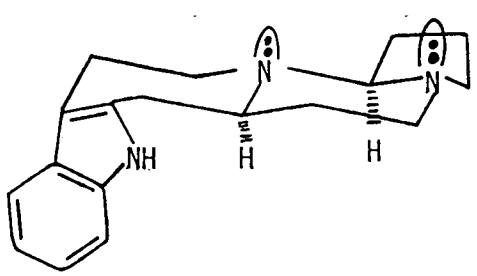


(39)

Of the three isomeric elaeokanidine alkaloids, only elaeokanidine A has been assigned a structure (40). The PMR spectra have shown the same relative stereochemistry for both elaeokanidine A and elaeokanine D. Elaeokanidines B and C closely resemble elaeokanidine A and both show IR bands at 1705 cm^{-1} (C=O) and 3440 cm^{-1} (NH). The PMR spectra also show close similarity, but their stereochemistry could not be determined.



(40)

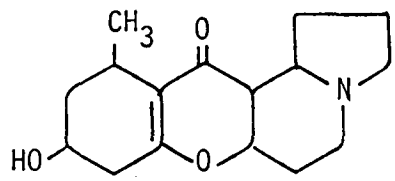


(41)

Elaeocarpidine (41) is the only indole alkaloid isolated from *Elaeocarpus* species. The structure of the carbon skeleton of elaeocarpidine was established by both degradative and spectroscopic studies.[36,37] The stereochemistry shown was preferred on conformational grounds,[37] and was supported by further spectroscopic

studies.[40] This structure was finally proved by three syntheses.[40,41,55]

In addition to (±)-elaeocarpine and (±)-isoelaeocarpine, another new indolizidine alkaloid, rudrakine (53) has been isolated from the leaves of the Indian Elaeocarpus species *E. ganitrus* Roxb..[50*] The structure of rudrakine was determined on the basis of its mass spectral fragmentations and the similarity of its infrared and ultraviolet spectra with those of pseudoepi-isoelaeocarpiline (33). Its stereochemistry has not been determined.



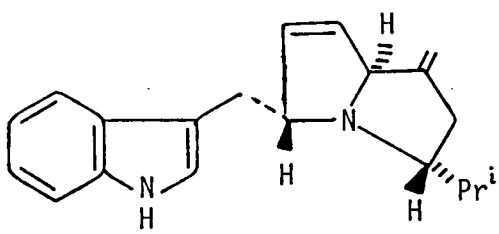
(53)

*However, *E. sphaericus* (Gaertn.) K. Schum. has been reported to be synonymous with *E. ganitrus* Roxb..[50]

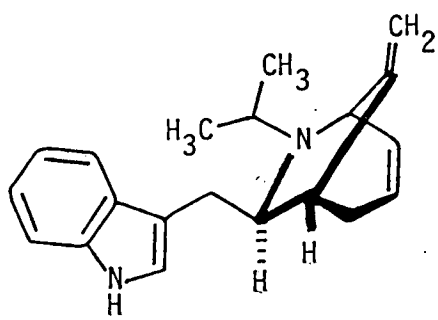
1.B.2. Aristotelia Alkaloids

The genus *Aristotelia* has fifteen species found only in the Southern hemisphere, more particularly in Australia, New Zealand, Chile, Peru and Argentina. Of these fifteen species only four have given positive tests for alkaloids.

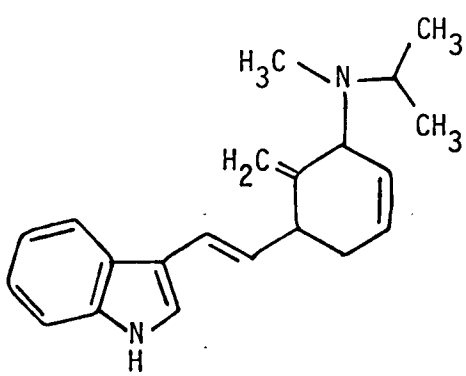
Bick[42] first reported the isolation of peduncularine as an indole-pyrrolizidine base (42) from a Tasmanian plant *Aristotelia peduncularis*. The structure was later modified to the indole base (43) on the basis of spectroscopic studies and degradative experiments.[43] The Hofmann degradation product of peduncularine was shown to be (44) and on catalytic hydrogenation, peduncularine yielded a compound which was characterised as (45) by spectroscopic means.



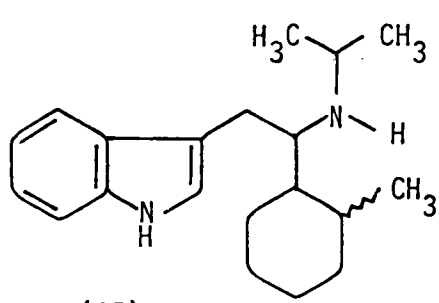
(42)



(43)

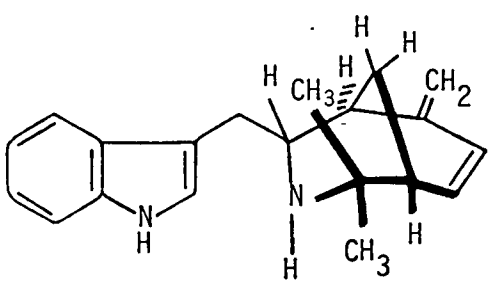


(44)

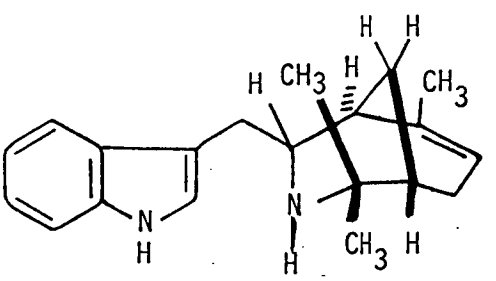


(45)

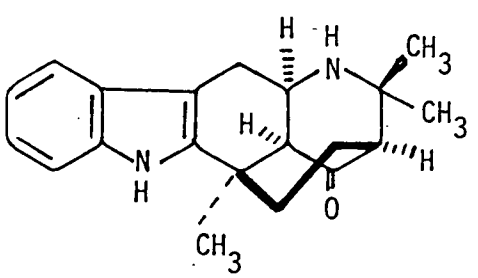
The minor alkaloid, sorelline, isomeric with peduncularine has been assigned the structure (46) on the basis of spectroscopic data.[44] The third alkaloid, hobartine, also a minor constituent, has two more hydrogens than either sorelline or peduncularine. It resembles the other two in having the indolic C-2 position unsubstituted. The presence of only one olefinic proton and the chemical shift of the single methyl group suggested that its structure was (47). This structure was finally proved by decoupling experiments and by a study of its mass spectral fragmentation pattern (Scheme 3).[44] The fourth alkaloid, aristoserratine, which also occurs in the N.Z. plant *A. serrata,* is a minor base and its structure has been determined by spectroscopic studies.[45] The absolute stereochemistry has been shown to be (48) by a comparison of the CD curves of aristoserratine and aristoteline (49).



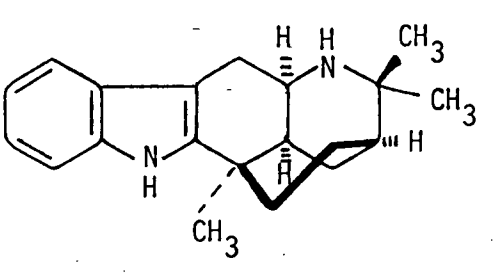
(46)



(47)

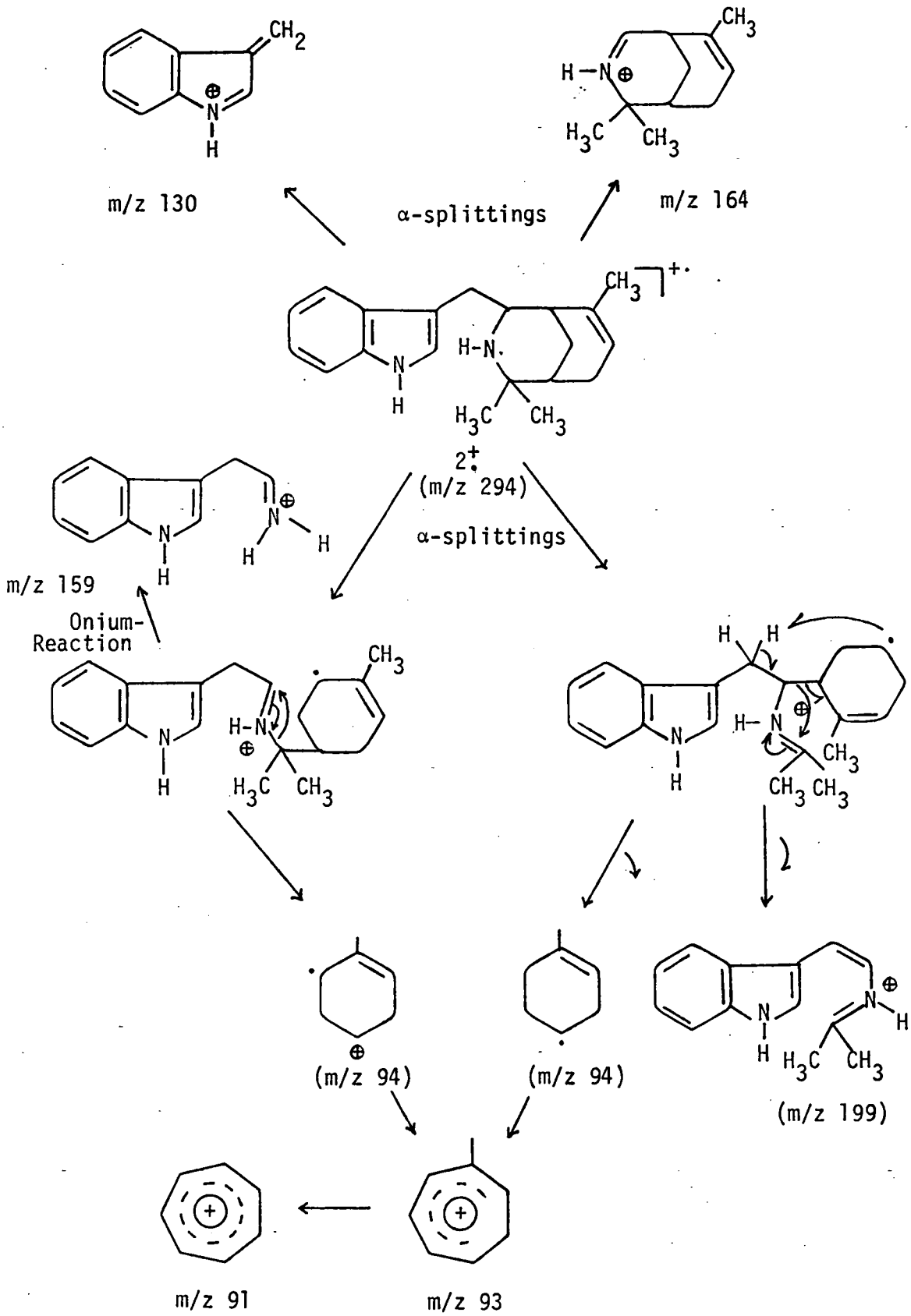


(48)

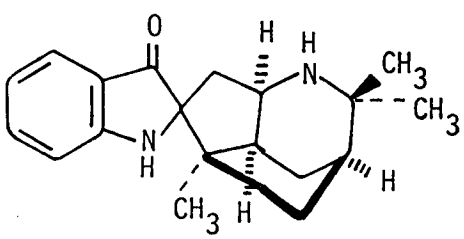


(49)

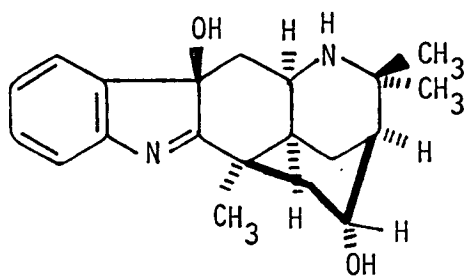
Scheme 3


m/z 130
α-splittings
m/z 164
(m/z 294)
α-splittings
m/z 159
Onium-
Reaction
(m/z 94)
(m/z 94)
(m/z 199)
m/z 91
m/z 93

The major alkaloid of the N.Z. plant *A. serrata* was found to be aristoteline (49). Its structure and absolute stereochemistry were determined by X-ray crystallographic studies.[46] Later, it was also isolated from the Chilean plant *A. chilensis* by Silva and others.[47] Three minor alkaloids isolated from *A. chilensis* were aristotelone[47] (50), aristotelinine[48] (51) and aristone[48,49] (52). The structure of aristotelone was determined by spectroscopic studies, whereas X-ray crystallographic analysis[48] was used to determine the structures of aristotelinine and aristone.



(50)



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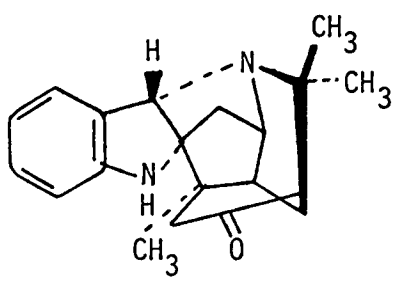

(52)

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CHAPTER 2

Alkaloids of *Aristotelia serrata* (W.R.B. Oliver)

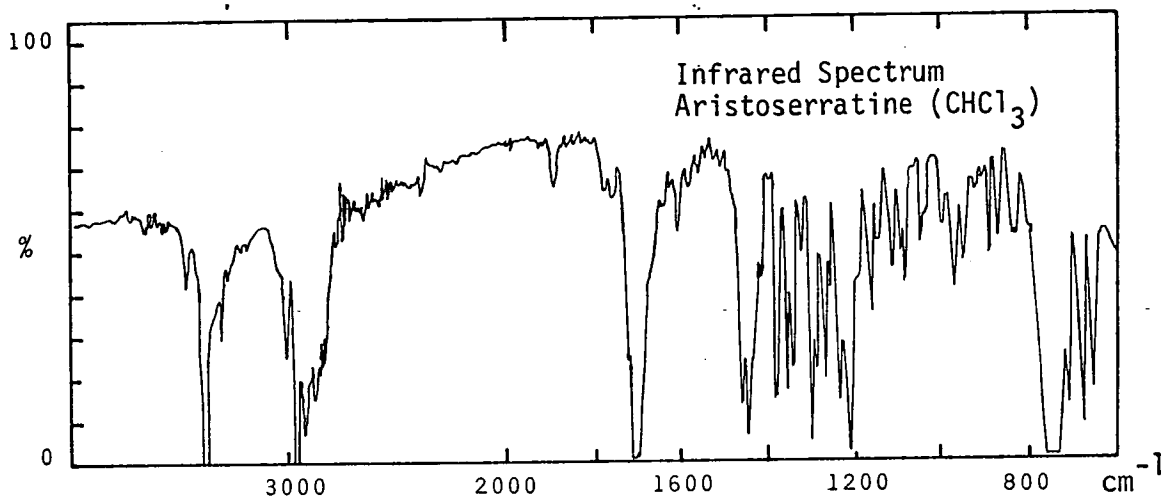
I. Results and Discussion

Aristotelia serrata is a small tree growing up to 10 metres in height, and abundant throughout New Zealand. The plant material, roots, stems and leaves (5.5 Kg), were collected from around Rotorua in the North Island. Extraction by standard methods yielded about 11.6 g (0.21%) of crude alkaloids. This mixture was separated into fourteen fractions of different basicities by Craig countercurrent distribution between chloroform and dilute sulphuric acid. After purification of each of these fractions by preparative thin-layer chromatography (p.t.l.c.) a total of fourteen bases were isolated. The major alkaloid, aristoteline, was isolated earlier and its structure and absolute stereochemistry were determined by X-ray crystallographic studies.[11] The rest of the alkaloids were present as minor bases.

1. The Structure of Aristoserratine

The minor base, aristoserratine crystallises from methanol as colourless square prisms, m.p. 199°C, $[\alpha]_D^{19}$ + 22.5° ($CHCl_3$). High-resolution mass spectrometry indicates a molecular formula of $C_{20}H_{24}N_2O$, which has been confirmed by elemental analysis. From its ultraviolet spectrum (Figure 2) aristoserratine has an indole nucleus substituted at C-2 and C-3 from the negative Ehrlich test. This substitution is confirmed by the P.M.R. spectrum. The infrared spectrum (Figure 1) shows two N-H stretchings (3473 cm^{-1} and 3330 cm^{-1})

Figure 1.



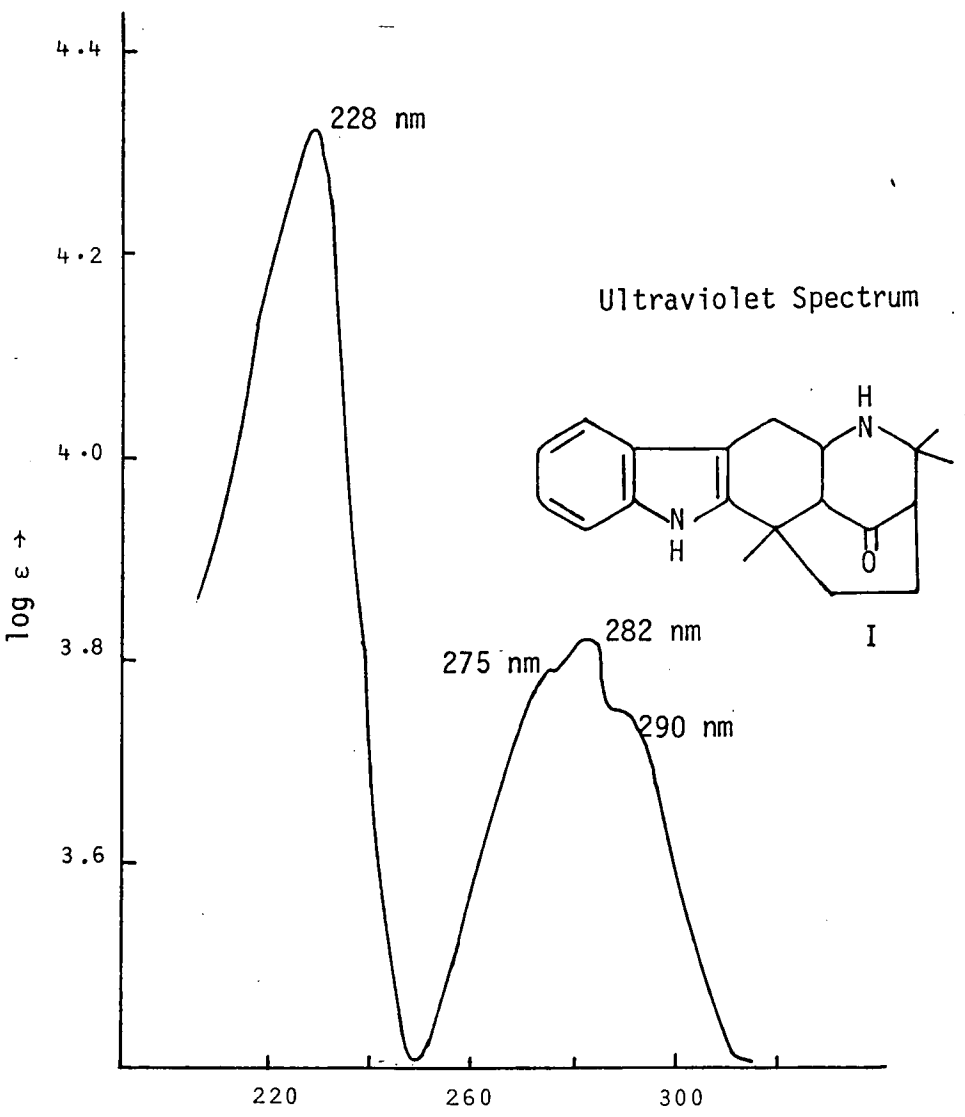
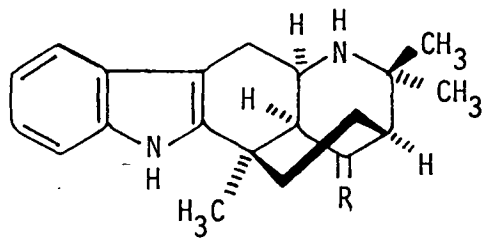


Figure 2.

and one ketone group (1710 cm^{-1}). On reduction with sodium borohydride, a dihydro-product (III) is obtained which shows no absorption around 1700 cm^{-1} in its infrared spectrum. The P.M.R. spectrum of aristoserratine has two singlets of three methyl groups at 1.38 (3H) and 1.19 (6H) ppm indicating the presence of one methyl group and a pair of geminal methyl groups respectively. The aliphatic nitrogen is secondary as is shown by the presence of an exchangeable proton signal at ca. 1.5 ppm.



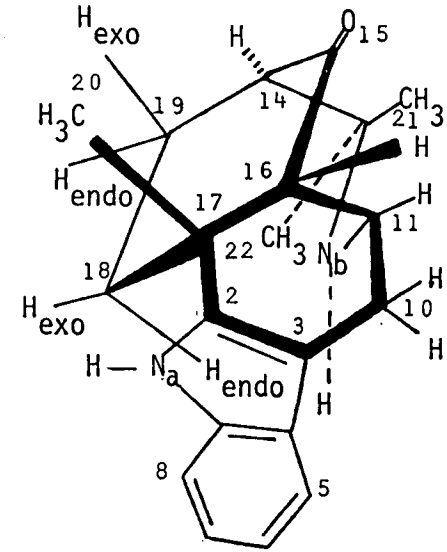
		R
I.	Aristoserratine	O
II.	Aristoteline	H,H
III.	Dihydroaristo-serratine	H,OH

The aliphatic nitrogen is evidently in the part-structure Ar-CH_2-CH-NH: each of the geminal protons resonating at 3.08 (H_{exo}-C_{10}) and 2.80 ppm (H_{endo}-C_{10}) appears as a doublet of doublets, and is coupled to the methine proton (H-C_{11}) at 3.79 ppm. This methine proton is again coupled to another methine proton appearing at 2.35 ppm (H-C_{16}, J = 2.5 Hz). From the intense M, M-CH_3 and M-C_3H_7N ions (Scheme 1) in the mass spectrum, it appears that the part structure can be extended to Ar-CH_2-CH-NH-C(Me)$_2$.

The sequence of all the aliphatic protons attached to a chain of carbon atoms extending from C-10 to C-19 has been established by their chemical shifts, multiplicities and coupling constants (Table I), and by a series of decoupling experiments.

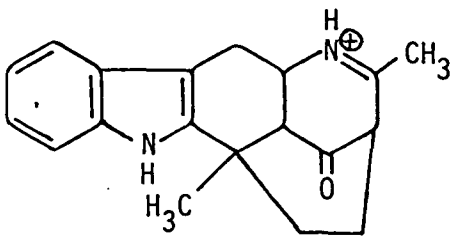
There is a geminal coupling (J = 13.8 Hz) between the protons at 2.58 ppm (H_{endo}-C_{18}) and 1.65 ppm (H_{exo}-C_{18}), each of which is further coupled to a pair of methylene protons at 2.18 (H_{endo}-C_{19}) and 1.92 ppm

Table I. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic protons in the pmr spectrum of Aristoserratine (I).

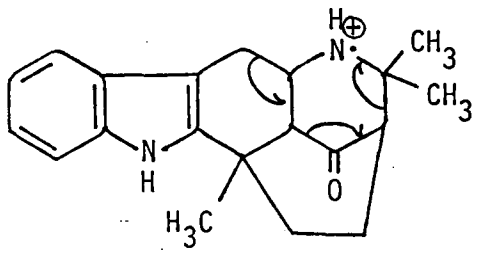


Protons	H_{exo}-C(10)	H_{endo}-C(10)	H-C(11)	H-C(16)	H-C(14)	H_{exo}-C(19)	H_{endo}-C(19)	H_{exo}-C(18)	H_{endo}-C(18)	Multiplicities	Chemical shifts
H_{exo} -C(10)		16.8	5.7							dd	3.08
H_{endo}-C(10)	16.8		1.5							dd	2.80
H-C(11)	5.7	1.5		2.5						ddd	3.79
H-C(16)			2.5		1.3					dd	2.35
H-C(14)				1.3		3.8	2.5			ddd	2.08
H_{exo}-C(19)					3.8		14.2	5.6	13.8	dddd	1.92
H_{endo}-C(19)					2.5	14.2		2.0	5.8	dddd	2.18
H_{exo} -C(18)						5.6	2.0		13.8	ddd	1.65
H_{endo}-C(18)						13.8	5.8	13.8		td	2.58

Scheme 1

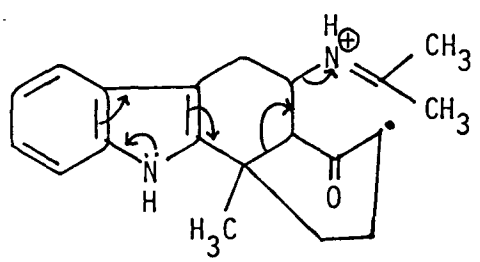


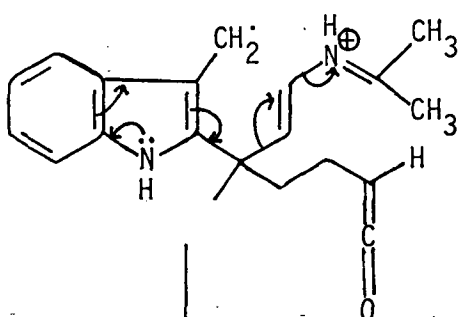
m/e 293

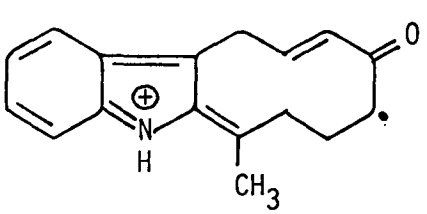


I. $M^{+\cdot}$ (m/e 308)

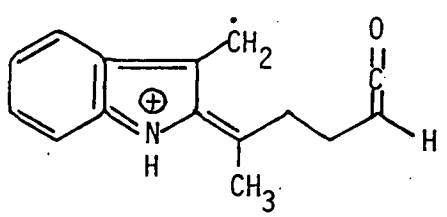
α-cleavage







m/e 251



m/e 225

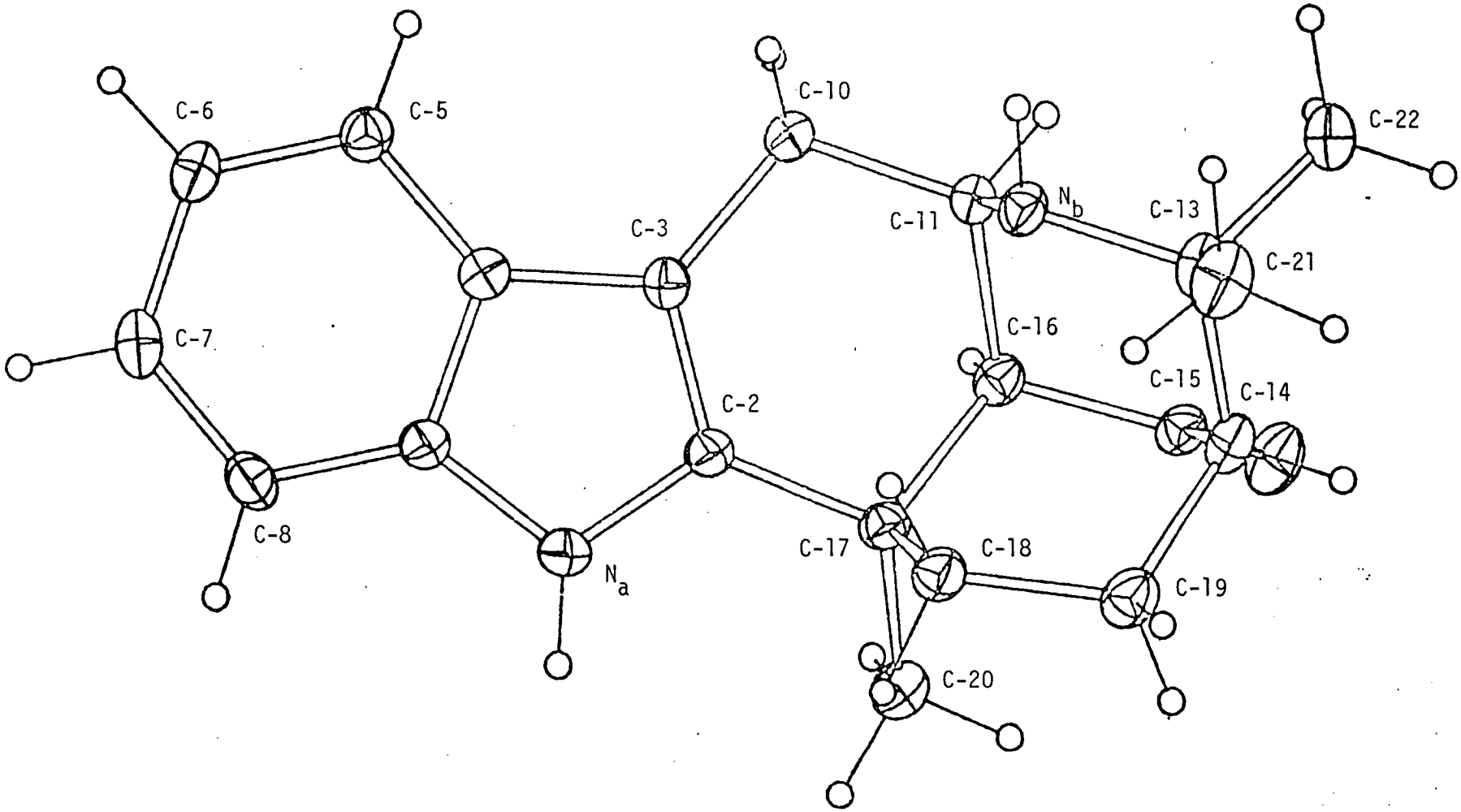


Figure 2a. X-Ray crystal structure of aristoserratine.

(H_{exo}-C_{19}, J_{gem} = 13.8 Hz). Each of the last two protons is again coupled to one other proton at 2.08 ppm (H-C_{14}). The coupling between the vicinal protons H_{endo}-C_{18} and H_{exo}-C_{19} ($J_{vic.}$ = 13.8 Hz) shows that they are disposed *trans*-diaxially. The carbonyl group must then be flanked by the protons H-C_{14} and H-C_{16} which show a long-range coupling[1] of 1.3 Hz. On the basis of these data, Structure (I) is suggested for aristoserratine.

The mass spectral fragmentation pattern (Scheme I) is in accord with this structure. The structure has been confirmed by X-ray crystallography,[2] which also established the relative stereochemistry. The absolute stereochemistry has been determined by a comparison of the CD curves of aristoserratine and aristoteline (II).[3] The X-ray crystallographic structure is shown in Figure 2a.

2. Aristotelinone

Another minor alkaloid, aristotelinone, crystallised from methanol in fine needles, changing around 255° into longer needles which remain unaltered up to 320°, $[\alpha]_D^{19}$ + 122.7° (MeOH + $CHCl_3$ 1:1). From mass spectrometry and elemental analysis it has been found to be an isomer of aristoserratine (I), with the molecular formula $C_{20}H_{24}N_2O$. Its ^{13}C N.M.R. spectrum shows a singlet at 195.5 ppm due to a carbonyl group, which from the strong infrared absorption at 1610 cm^{-1} (nujol) (Figure 3) and ultraviolet absorption (Figure 4) maximum at 301 nm (MeOH) seems to be attached to the 3-position of an indole nucleus.[4] In accord with this, the P.M.R. and ^{13}C N.M.R. spectra lack the signals for a methylene group at the allylic position. A doublet from a single proton at 3.64 ppm (J = 3.1 Hz) in the P.M.R. spectrum could then be attributed to a methine proton on a carbon (C-11) α- to the aliphatic nitrogen. This proton is coupled to the adjacent methine proton at 1.98 ppm (H-C_{16}).

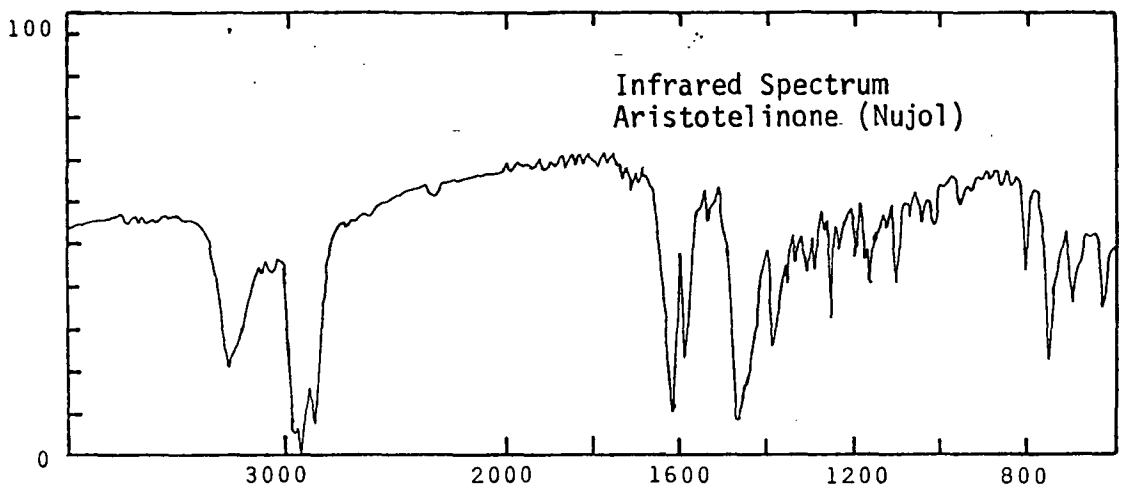


Figure 3.

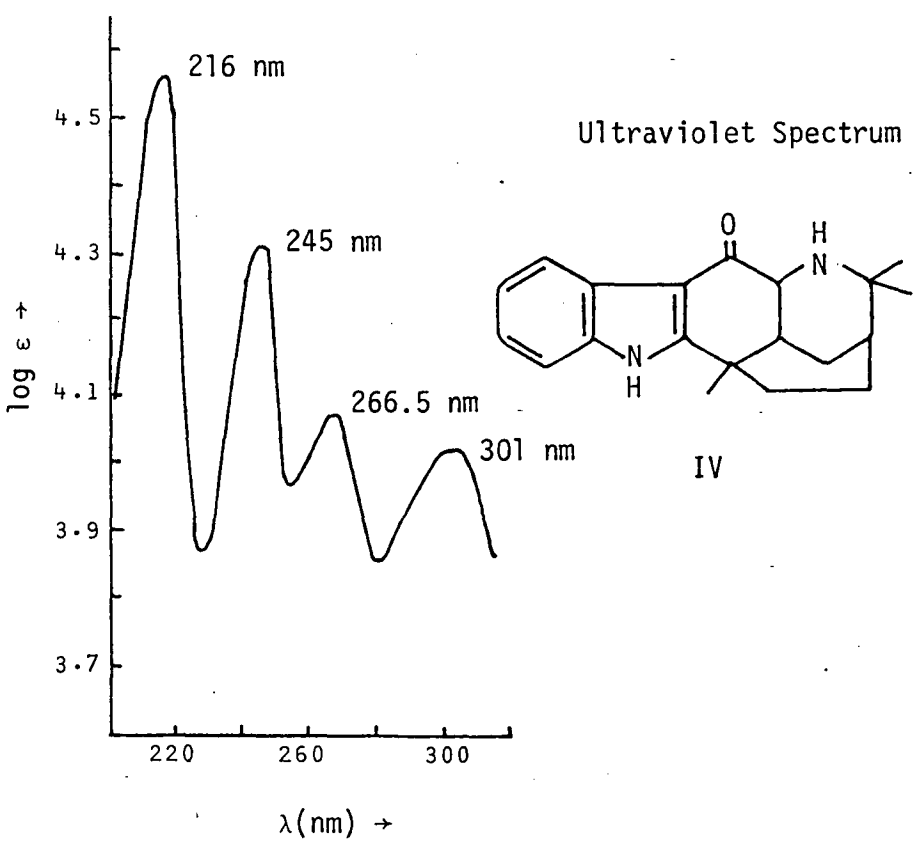
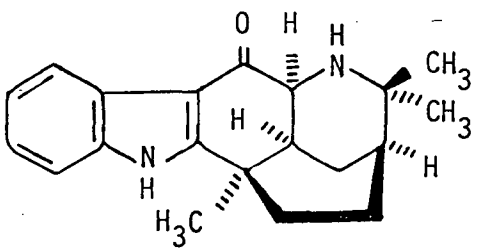
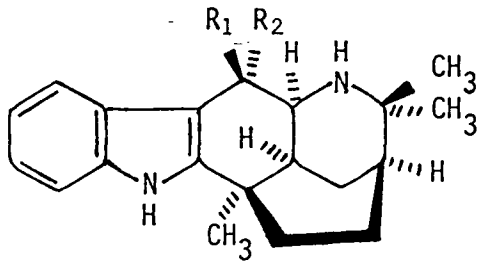


Figure 4.

Like aristoteline (II), aristotelinone also shows three high-field singlets due to three C-methyl groups. From both P.M.R. and ^{13}C N.M.R. spectra, the 2- and 3- positions of the indole nucleus appear to be substituted, and this is confirmed by a negative Ehrlich test. Thus the structure (IV) is tentatively assigned to aristotelinone.



IV



	R_1	R_2
V. Epi-dihydroaristotelinone	OH	H
VI. Dihydroaristotelinone	H	OH

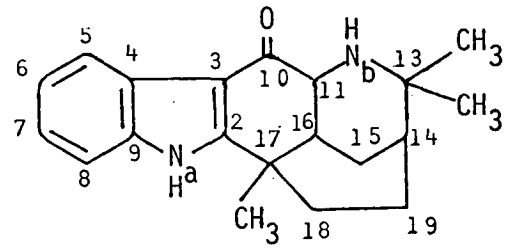
All the carbons can be accounted for in the ^{13}C N.M.R. spectrum. The chemical shifts, multiplicities and assignments are presented in Table II. The carbon-assignments are based on related systems.[5-8]

On reduction with sodium borohydride, aristotelinone gives a single product with the formula $C_{20}H_{26}N_2O$, as determined by high resolution mass spectrometry. This dihydroaristotelinone is further reduced[16] with lithium aluminium hydride to give aristoteline, thus showing its structure as either (V) or (VI). Unlike (VI), V has, however, a strong M-18 peak (m/e 292) in its mass spectrum indicating that the hydroxyl group on C-10 and the proton on C-11 in V have a *trans*-configuration. Therefore, the $NaBH_4$-reduction product can be assigned the structure (V).

On the other hand, direct reduction of aristotelinone with lithium aluminium hydride gives a pair of alcohols (V and VI) epimeric at C-10, and a third crystalline compound which proved to be identical with aristoteline; the structure and absolute stereochemistry of aristotelinone is thus established as IV.[12]

Table II

C-13 Chemical shifts of Aristotelinone (measured in $CDCl_3$ + CD_3OD)

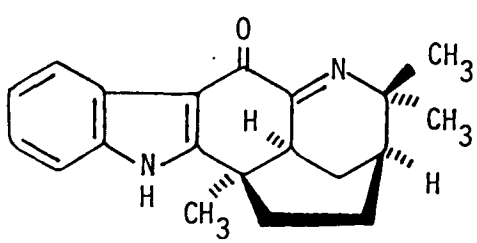


Carbon	2	3	4	5	6	7	8	9	10	11	13	14	15	19	16	17	18	20	21	22
TMS δ_{ppm}	162.6	109.0	127.0	121.8	123.5	122.7	111.9	139.0	195.5	61.0	53.3	37.0	26.1	25.0	41.4	35.5	34.4	22.9	29.4	27.3
Multiplicity	s	s	s	d	d	d	d	s	s	d	s	d	t	t	d	s	t	qa	qa	qa

3. Makonine

Makonine was crystallised from methanol as hexagonal crystals, m.p. 310-312°C (d), $[\alpha]_D^{19}$ + 431.1° (MeOH + $CHCl_3$ 1:2). High-resolution mass spectrometry and elemental analysis gave a molecular formula $C_{20}H_{22}N_2O$, with two hydrogens less than aristotelinone. This base must thus have either one more unit of unsaturation or an extra ring system.

Like aristotelinone (IV), makonine also has a carbonyl group attached to the 3-position of the indole nucleus as is shown by a strong absorption band at 1610 cm^{-1} in the infrared spectrum (Figure 5) and a λ_{max} at 314 nm (log ε 4.37) in the ultraviolet absorption spectrum (Figure 6). Its ^{13}C N.M.R. spectrum is similar to that of aristotelinone, and shows a singlet at 186.2 ppm due to the carbonyl group. However, it shows an additional quaternary carbon at 170.5 ppm but lacks a signal for the methine carbon next to the non-indolic nitrogen. Moreover, the P.M.R. spectrum shows neither a low field signal for the methine proton (H-C_{11}) nor any exchangeable proton attached to the non-indolic nitrogen. Like aristoteline (II), makonine gives a negative Ehrlich test, and its N.M.R. spectra show the presence of a pair of geminal dimethyl groups, plus an extra methyl group attached to a quaternary carbon.



VII

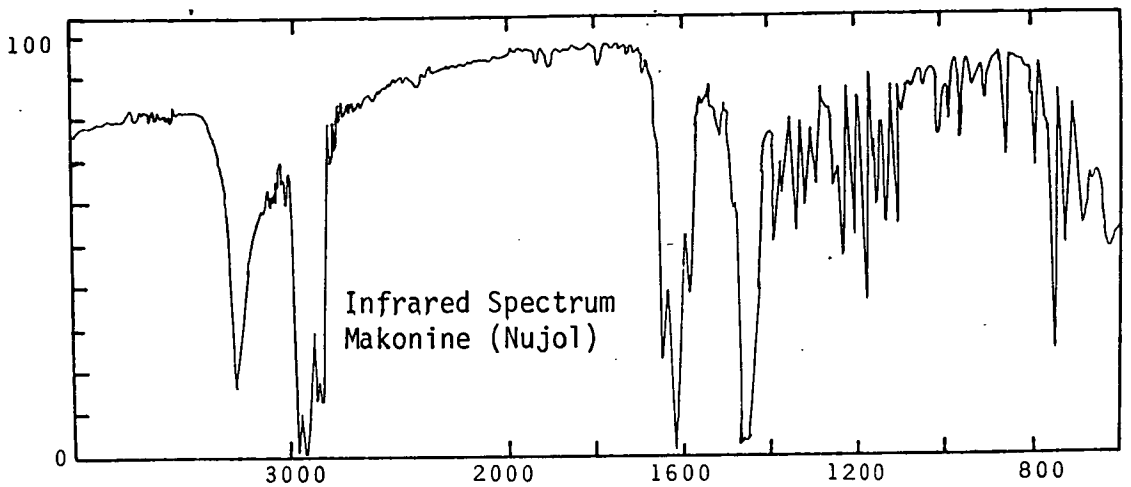


Figure 5.

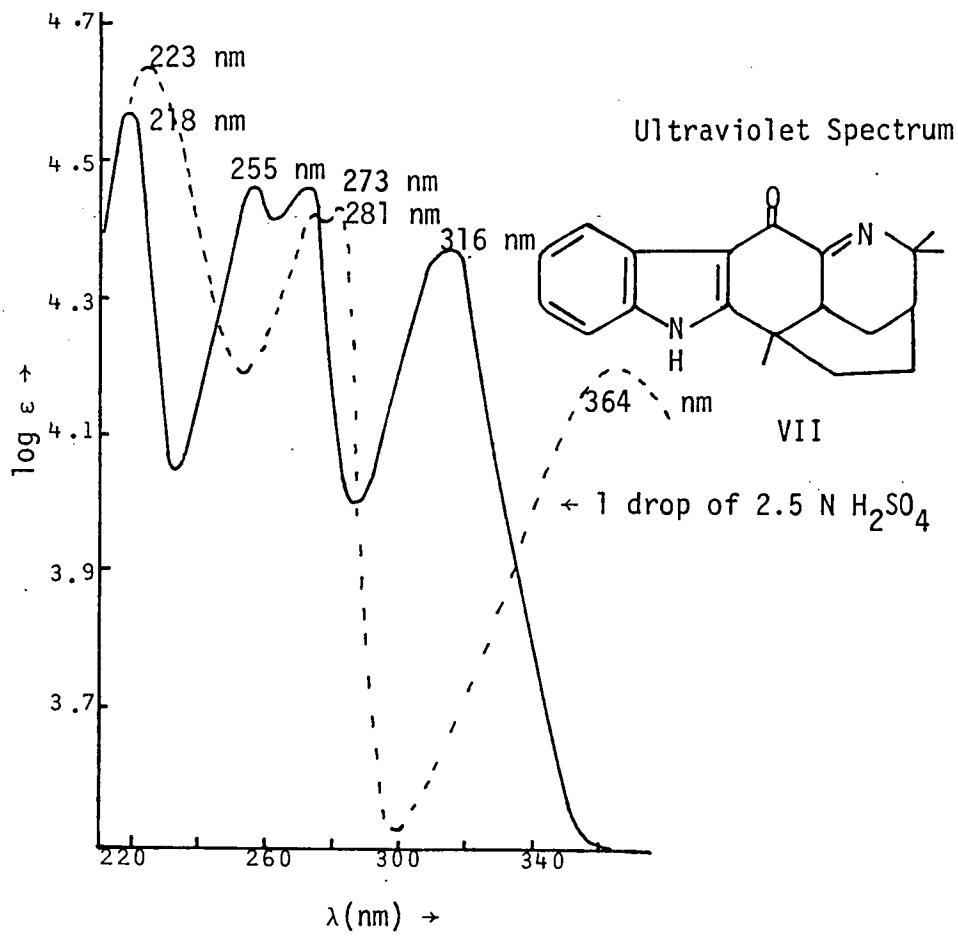
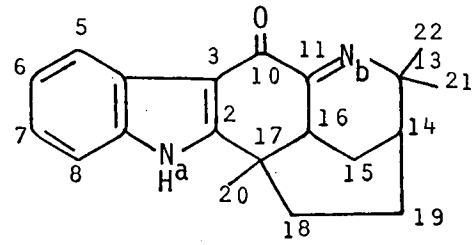


Figure 6.

Table III

C-13 Chemical shifts of Makonine (measured in $CDCl_3$ + CD_3OD)



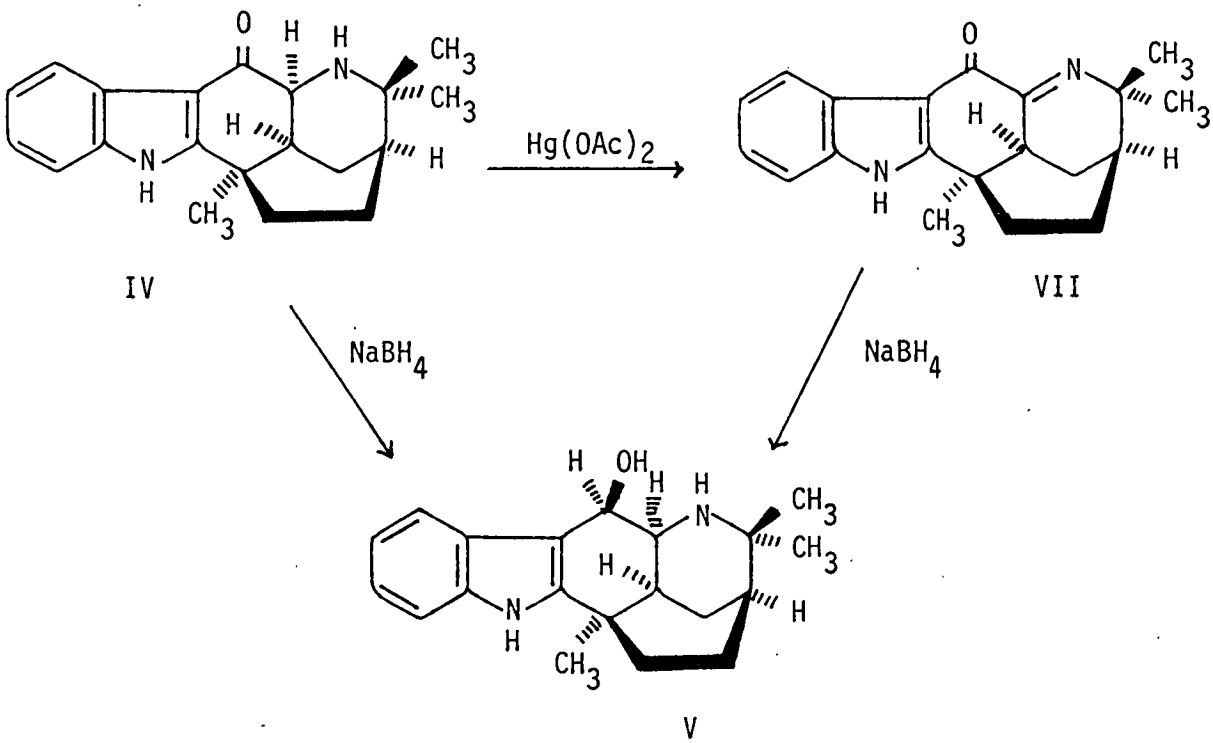
Carbon	2	3	4	5	6	7	8	9	10	11	13	14	15	19	16	17	18	20	21	22
δ^{TMS}_{ppm}	161.5	112.0	125.0	121.6	123.9	123.0	121.1	137.2	186.2	170.5	58.6	36.3	24.3	21.5	45.7	40.5	33.3	19.3	29.9	27.0
Multiplicity	s	s	s	d	d	d	d	s	s	s	s	d	t	t	d	s	t	qa	qa	qa

On reduction with sodium borohydride, makonine gave a tetrahydro-compound as a major product, which proved identical to the epi-dihydro-aristotelinone (V) (Scheme 2). Thus a tentative structure (VII) could be assigned to makonine.

All the carbons in structure VII can be accounted for in the ^{13}C N.M.R. spectrum. The chemical shifts, multiplicities and assignments are presented in Table III.

Finally structure VII was confirmed by conversion of aristotelinone (IV) into makonine in 25% yield by mercuric acetate oxidation (Scheme 2). This experiment also established the absolute stereochemistry, as shown in VII.

Scheme 2



IV VII V

4. Serratenone

Serratenone was isolated in 0.003% yield from the dry plant material and has $[\alpha]_D^{19}$ - 45.3° ($CHCl_3$). The ultraviolet absorption spectrum (Figure 8) indicates the presence of an indole nucleus. High-

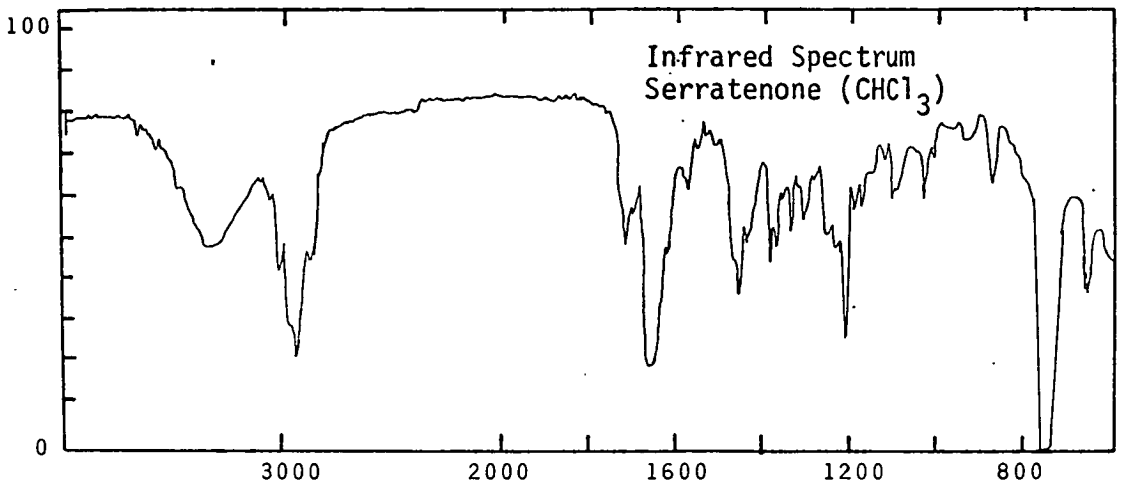


Figure 7.

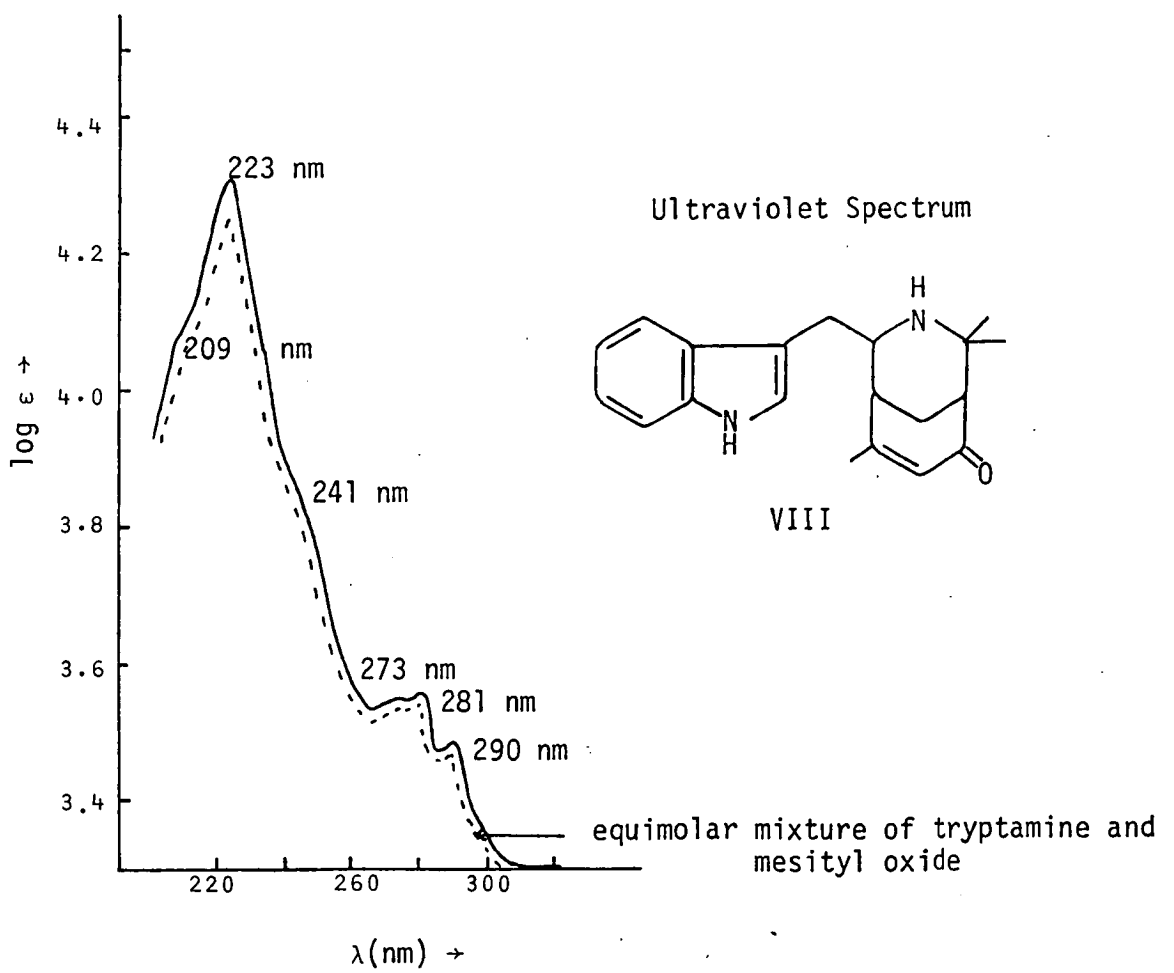
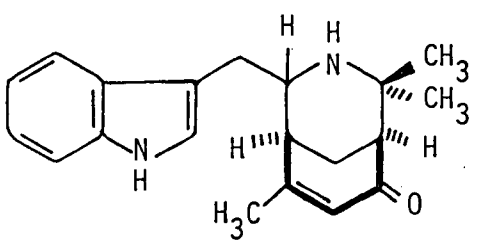


Figure 8.

resolution mass spectrometry gives the same formula $C_{20}H_{24}N_2O$ for serratenone as for aristoserratine (I) or aristotelinone (IV). However, serratenone has one less ring, since it shows an olefinic proton ($H\text{-}C_7$) signal at 6.06 ppm in its P.M.R. spectrum (Figure 9). The latter spectrum, moreover, reveals a signal at 7.12 ppm corresponding to a proton attached to C-2' of the indole ring. A positive Ehrlich test supports the conclusion that this position is free, which is further confirmed by the presence of two complementary ion peaks at m/e 130 and 178 (base peak) in its mass spectrum. The ultraviolet maximum at 241 nm and the strong infrared band at 1650 cm^{-1} (Figure 7) suggest that serratenone has an α,β-unsaturated ketone system, and in fact its ultraviolet absorption spectrum is practically identical with that of an equimolar mixture of tryptamine and mesityl oxide.



VIII

The sequence of protons in the aliphatic part of the molecule is deduced from the P.M.R. and mass spectra of serratenone. The chemical shifts, multiplicities and coupling constants of the protons are presented in Table IV.

The formation of strong ions at m/e 199 and 159 in the mass spectrum can be explained (Scheme 3) in the same way as for the mass spectral fragmentation of hobartine, thus pointing to the presence of the part structure: ArCH -CH-NH-C(Me)$_2$. Each of the methylene protons

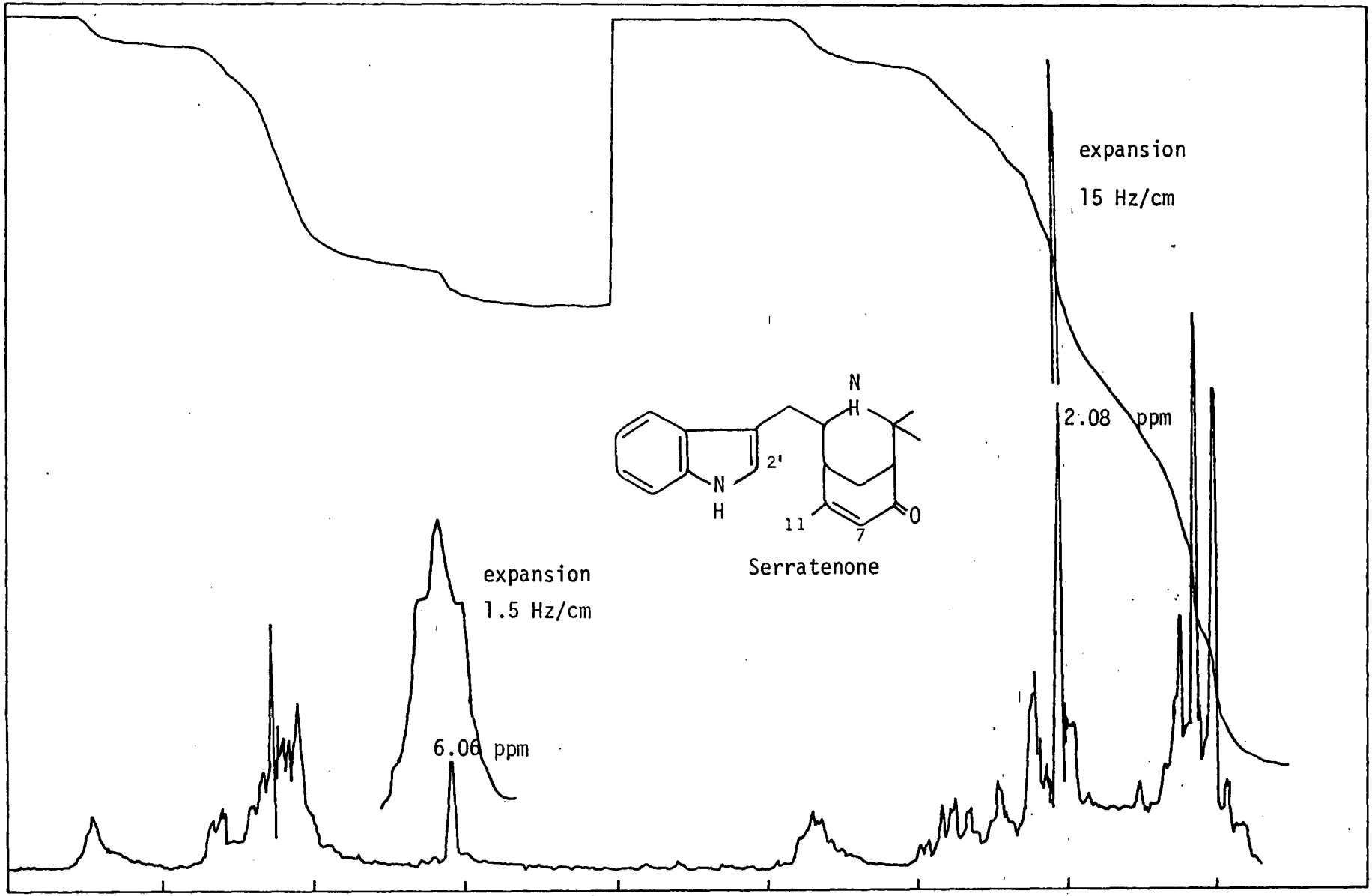
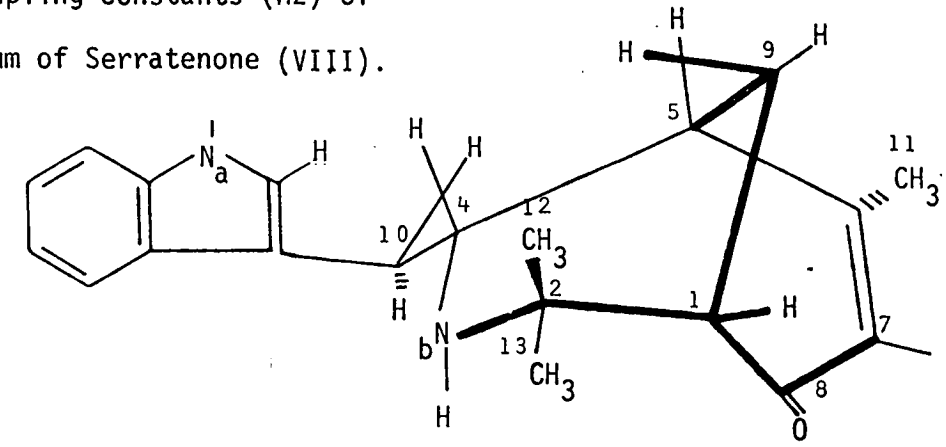

expansion
15 Hz/cm
2.08 ppm
N
H
2'
N
H
11
7
O
Serratenone
expansion
1.5 Hz/cm
6.06 ppm

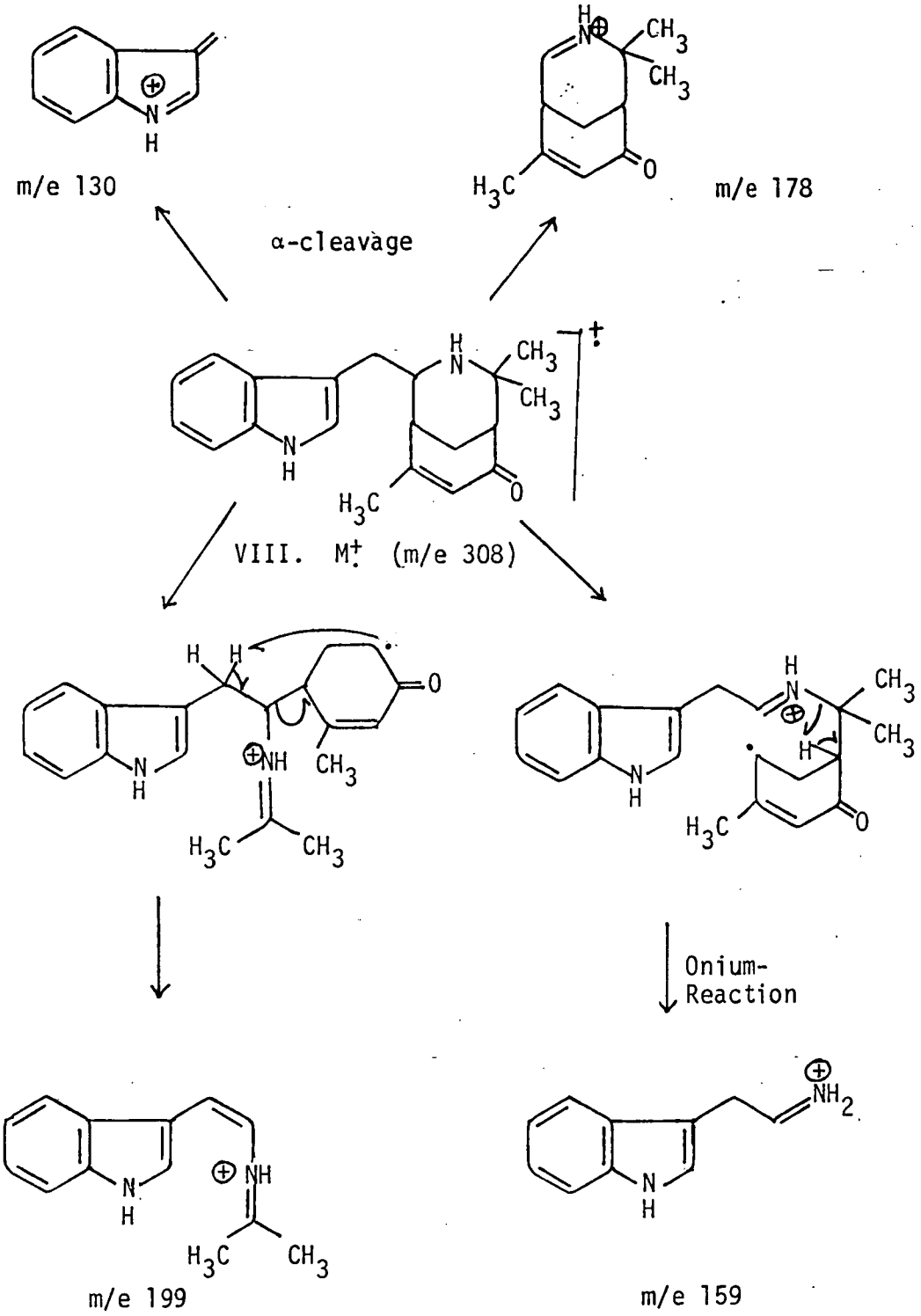
Figure 9

Table IV. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic and olefinic protons in the pmr spectrum of Serratenone (VIII).



Protons	H_a-C(10)	H_b-C(10)	H-C(4)	H-C(5)	H_a-C(9) + H_b-C(9)	H-C(1)	H-C(7)	3H-C(11)	Multipl-icities	Chemical shifts
H_a-C(10)		13.5	6.0						dxd	2.93
H_b-C(10)	13.5		7.5						dxd	2.65
H-C(4)	6.0	7.5		2.4					dxdxd	3.75
H-C(5)			2.4		2.4		1.0		qaxd	2.48
H_a-C(9) + H_b-C(9)				2.4		2.4			t	2.25
H-C(1)					2.4				t	2.00
H-C(7)				1.0				1.0	quintet	6.06
3H-C(11)							1.0		t	2.08

Scheme 3


m/e 130
α-cleavage
m/e 178
VIII. M+. (m/e 308)
Onium-
Reaction
m/e 199
m/e 159

(2.93 ppm, H_a-C_{10} and 2.65 ppm, H_b-C_{10}) appears as doublet of a doublet and is coupled to the methine proton (H-C_4) resonating at 3.75 ppm. This methine proton is again coupled to another methine proton (2.48 ppm, H-C_5, $J_{4/5}$ = 2.4 Hz), which in turn is coupled to a pair of geminal protons (2H-C_9) appearing as a two-proton triplet at 2.25 ppm (J = 2.4 Hz). These are further coupled (J = 2.4 Hz) to a third methine proton H-C_1 (2.00 ppm) which shows no other coupling and is assigned a location adjacent to the carbonyl group. The proton at 2.48 ppm is also coupled allylically ($J_{5/7}$ = 1.0 Hz) to the olefinic proton (H-C_7); the latter shows a similar allylic coupling to the protons of the methyl group (at 2.08 ppm, 3H-C_{11}) attached to the olefinic carbon. These data point to structure VIII for serratenone, which is in full accord with its mass spectrum.

5. Makomakine

Makomakine has a molecular formula $C_{20}H_{26}N_2$, established by high-resolution mass spectrometry. It crystallises from chloroform, on chilling, as colourless crystals, m.p. 99-100°C, $[\alpha]_D^{19}$ + 131.2° ($CHCl_3$). The ultraviolet absorption spectrum (Figure 11) shows it has an indole nucleus. From its molecular formula, makomakine is isomeric with aristoteline; however, its P.M.R. and ^{13}C N.M.R. spectra show that it has one olefinic bond in a vinylidine group. It thus has a two-ring system in addition to the indole nucleus. Makomakine gives a positive Ehrlich test, and a singlet at 6.95 ppm (H-C2') in its P.M.R. spectrum, together with the corresponding doublet at 122.4 ppm in the ^{13}C N.M.R. spectrum, indicates that the 2'-position of the indole nucleus is unsubstituted. On the other hand, the 3'-position evidently bears a methylene group from the strong m/e 130 peak in the mass spectrum,[9] and

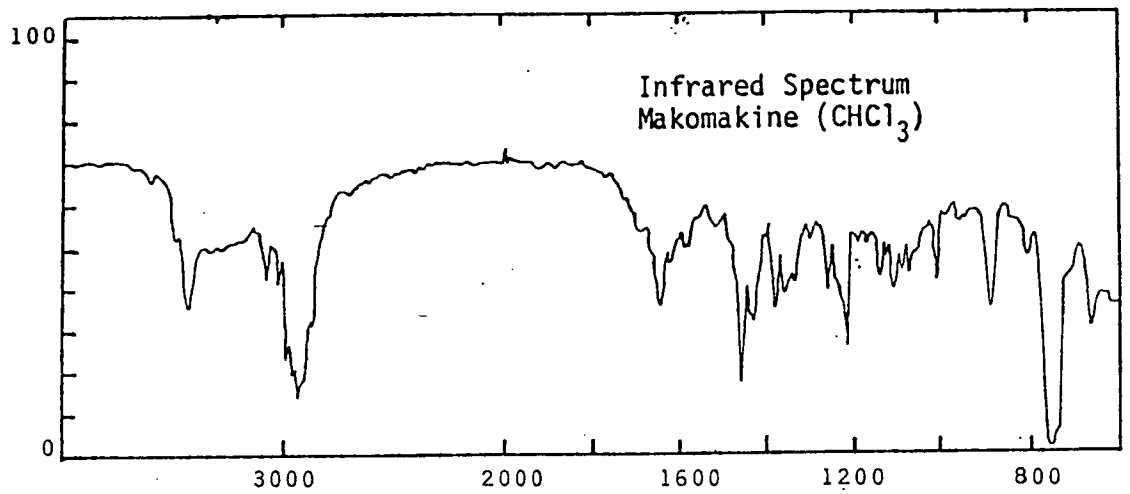
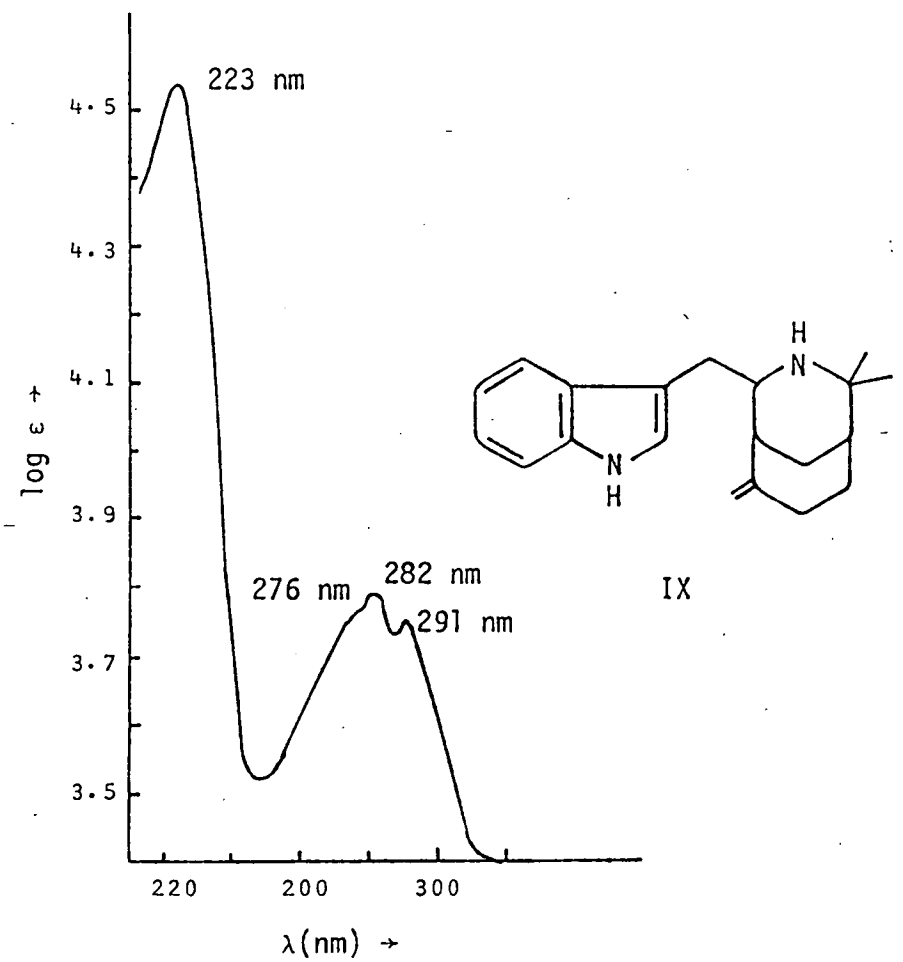


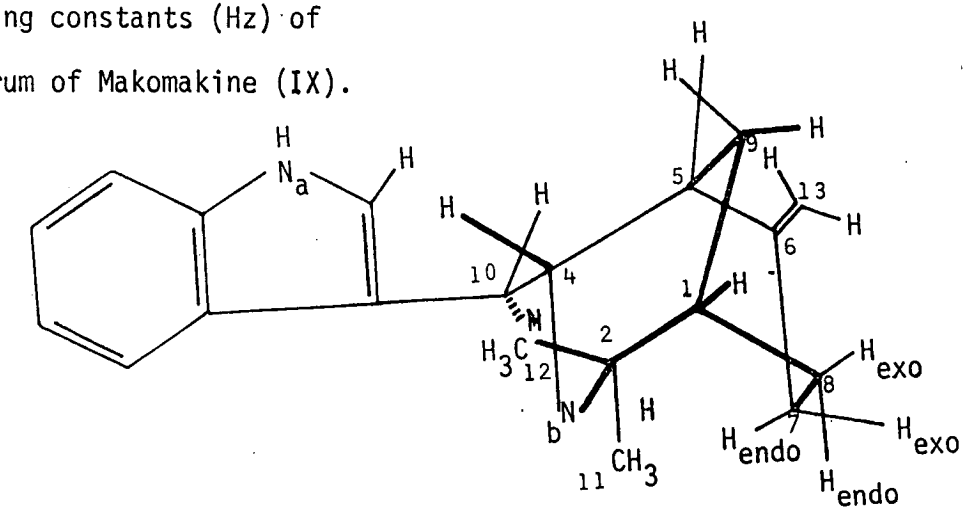
Figure 10.



IX

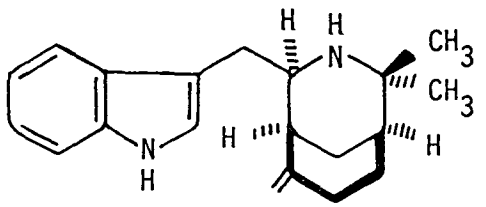
Figure 11

Table V. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic and olefinic protons in the pmr spectrum of Makomakine (IX).



Protons	H_a-C(10)	H_b-C(10)	H-C(4)	H-C(5)	H_a-C(9)	H_b-C(9)	H-C(1)	H_{exo}-C(8)	H_{endo}-C(8)	H_{exo}-C(7)	H_{endo}-C(7)	H_a-C(13)	H_b-C(13)	Multiplicities	Chem. shifts
H_a-C(10)		14.25	6.0											dxd	2.75
H_b-C(10)	14.25		7.6											dxd	2.70
H-C(4)	6.0	7.6		2.7										dxdxd	3.48
H-C(5)			2.7		2.7	2.7								qa	2.26
H_a-C(9)				2.7		12.7	2.7							dxt	1.57
H_b-C(9)				2.7	12.7										
H-C(1)					2.7										
H_{exo}-C(8)											14.2				
H_{endo}-C(8)											6.7				
H_{exo}-C(7)											14.2				
H_{endo}-C(7)								14.2	6.7	14.2		2.45	2.45	txdxt	3.06
H_a-C(13)											2.45		2.55	dxd	4.78
H_b-C(13)											2.45	2.55		dxd	4.58

from the geminally-coupled pair of protons at 2.75 and 2.70 ppm in its P.M.R. spectrum.



IX

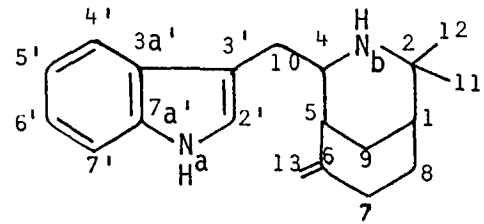
The same sequence $ArCH_2$-CH-NH-CMe_2 as for serratenone can be deduced from the P.M.R. spectrum, and also from strong ion peaks at m/e 199, 164 (base peak), 159 and 130 (Scheme 4) in the mass spectrum of makomakine. The P.M.R. spectrum also shows the presence of two exchangeable protons at 8.03 and 1.80 ppm.

The chemical shifts, multiplicities and coupling constants of the aliphatic and olefinic protons are presented in Table V.

The small coupling (J = 2.45 Hz) between the vinylidine protons and the proton at 3.06 ppm (H_{endo}-C_7) indicates that the latter is located at the allylic position. This proton is further coupled to three more protons with two large couplings of 14.2 Hz (one geminal with H_{exo}-C_7, and the other *trans*-vicinal with H_{exo}-C_8) and one medium coupling of 6.7 Hz (with H_{endo}-C_8). The quartet (J = 2.7 Hz) at 2.26 ppm is assigned to the proton on C-5, which shows coupling (J = 2.7 Hz) with the methine proton on C-4 and two other protons, which are present possibly as a methylene group. One of these methylene protons (H_a-C_9) appears at 1.57 ppm as a doublet of a triplet; it shows a large geminal coupling (J = 12.7 Hz), and a small coupling (J = 2.7 Hz) with the only other proton on C-1.

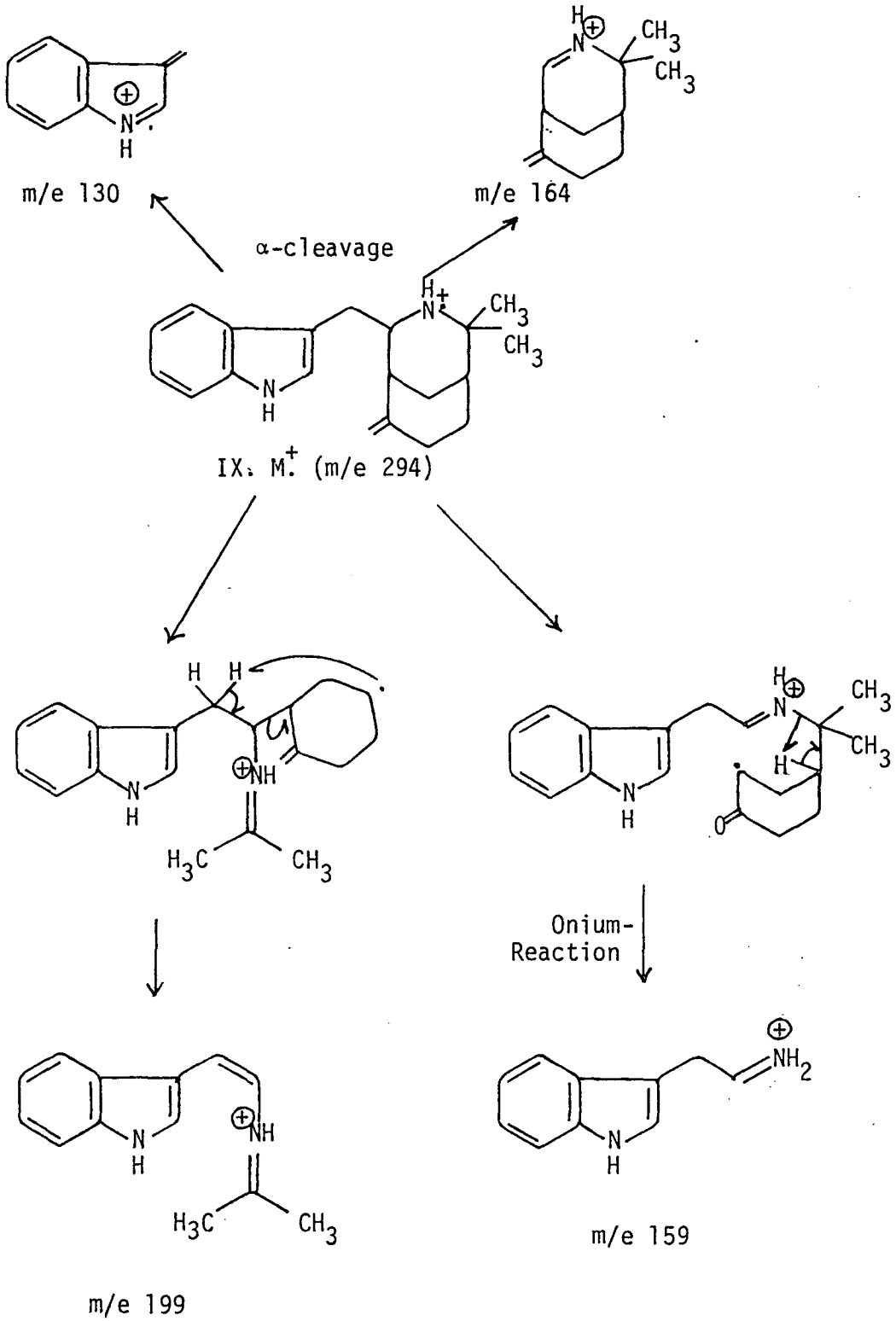
Table VI

C-13 Chemical shifts of Makomakine (measured in $CDCl_3$)

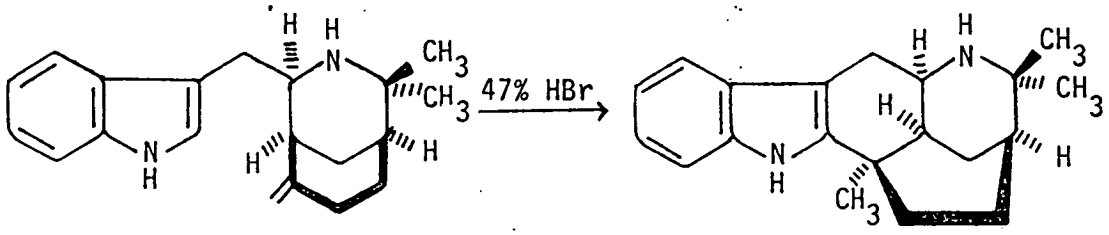


Carbon	2'	3'	3a'	4'	5'	6'	7'	7a'	1	2	4	5	6	7	8	9	10	11	12	13
δ^{TMS}_{ppm}	122.4	113.8	127.9	119.1	121.8	119.3	111	136.4	36.8	53.3	54.2	43.2	150.4	33.2	31.9	31.3	29.2	29.7	27.1	108.8
Multiplicity	d	s	s	d	d	d	d	s	d	s	d	d	s	t	t	t	t	qa	qa	t

Scheme 4


m/e 130
m/e 164
α-cleavage
IX. M.+ (m/e 294)
Onium-
Reaction
m/e 159
m/e 199

The evidence so far points to a structure IX for makomakine, which is supported by the ^{13}C N.M.R. data presented in Table VI.



IX II

Finally, an acid-catalysed rearrangement of makomakine to the naturally-occurring aristoteline confirmed structure IX, and established the absolute stereochemistry at the same time.

6. Aristoserratenine

Aristoserratenine is shown to be an isomer of aristoteline from its molecular formula, $C_{20}H_{26}N_2$, which was established by high-resolution mass spectrometry. However, its ultraviolet absorption maxima at 259 nm and 226 nm (Figure 13) shows it is an indolenine derivative.

The 2-position is definitely unsubstituted, as shown by the presence of a sharp singlet at 8.00 ppm in its P.M.R. spectrum and a doublet at 178.7 ppm in the ^{13}C N.M.R. spectrum. The other major difference in the latter spectrum is the shift to 70.8 ppm of a singlet normally appearing around 104 ppm in the case of aristoteline. This chemical shift (70.8 ppm) is assigned to the spiro-carbon at position C-3; the other two aliphatic quaternary carbons appear at 54.0 (C-13) and 46.8 (C-17) ppm.

The sequence of protons in the aliphatic part of the molecule has

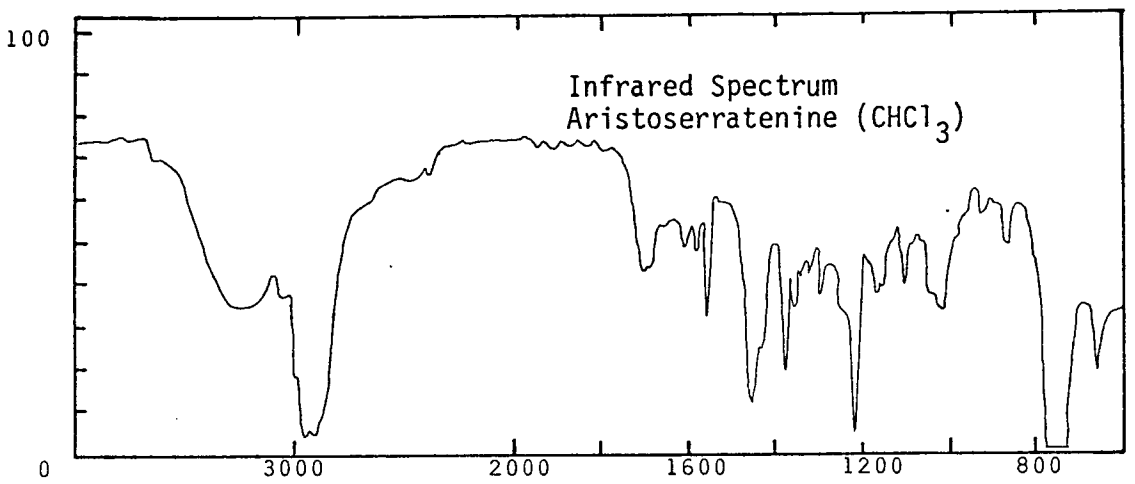


Figure 12.

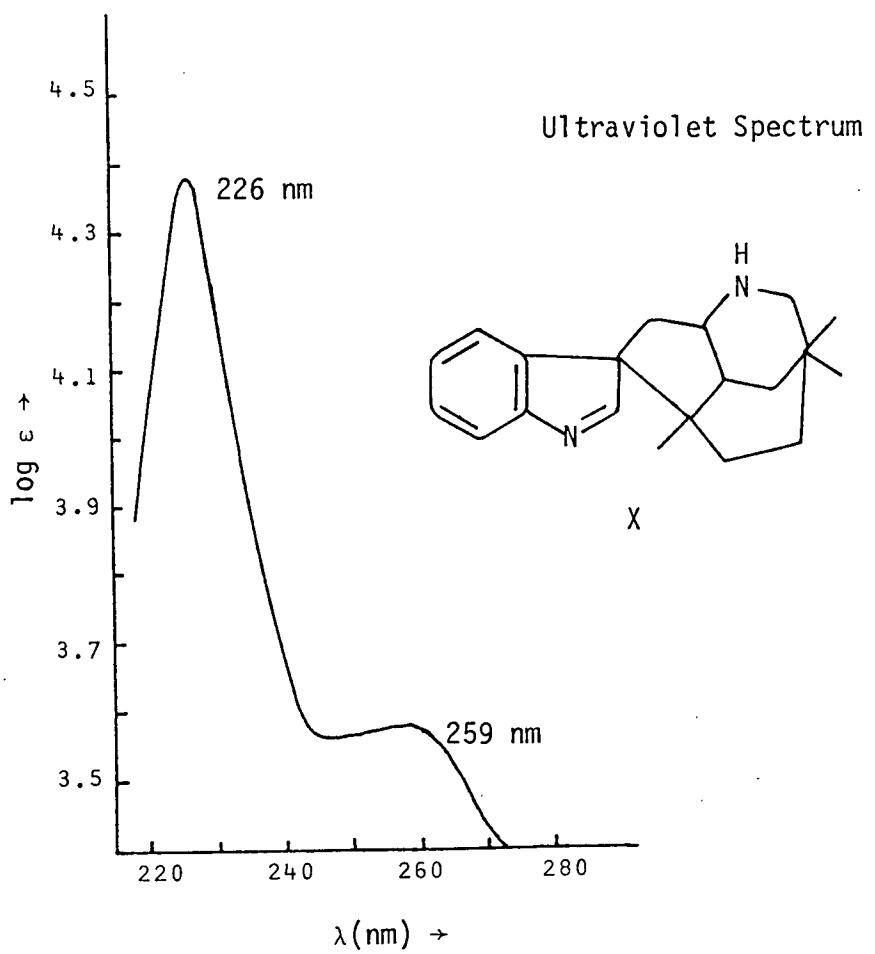
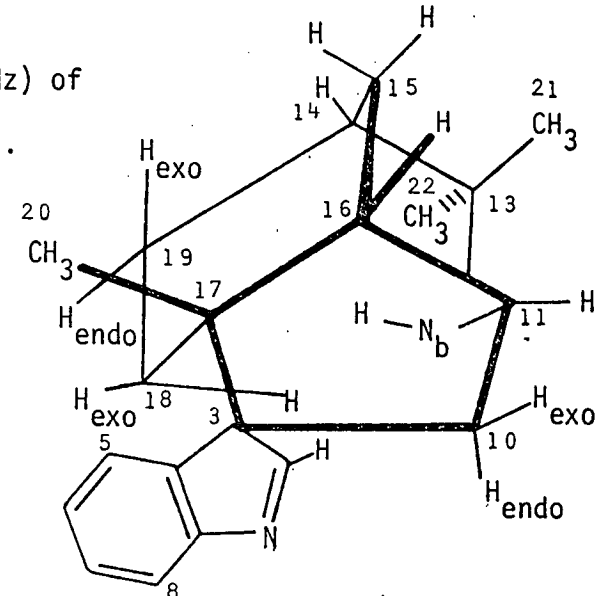


Figure 13.

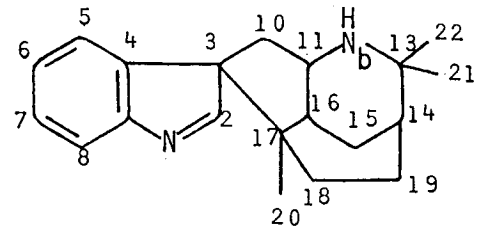
Table VII. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic protons in the pmr spectrum of Aristoserratenine (X).



Protons	H_{exo}-C(10)	H_{endo}-C(10)	H-C(11)	H-C(16)	H_a-C(15)	H_b-C(15)	H-C(14)	H_{exo}-C(19)	H_{endo}-C(19)	H_{exo}-C(18)	H_{endo}-C(18)	Multiplicities	Chemical shifts
H_{exo}-C(10)		14.7	6.6									dxd	2.37
H_{endo}-C(10)	14.7		0.9									dxd	1.87
H-C(11)	6.6	0.9		5.0								dxdxd	3.83
H-C(16)			5.0		2.5	2.5						dxt	2.02
H_a-C(15)				2.5		13.3	2.5		2.5			dxqa	2.17
H_b-C(15)				2.5	13.3		2.5					dxt	1.66
H-C(14)					2.5	2.5		2.5	2.5			quintet	1.39
H_{exo}-C(19)							2.5		14.0	5.0	14.0	txdxd	1.61
H_{endo}-C(19)					2.5		2.5	14.0		2.5	5.5	dxdxqa	1.99
H_{exo}-C(18)								5.0	2.5		14.0	dxdxd	1.00
H_{endo}-C(18)								14.0	5.5	14.0		txd	3.16

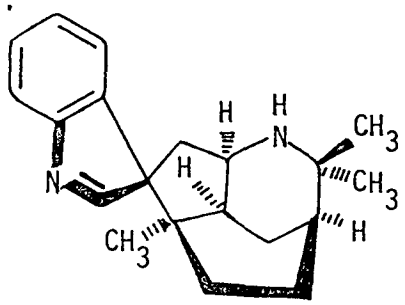
Table VIII

C-13 Chemical shifts of Aristoserratenine (measured in $CDCl_3$)



Carbon	2	3	4	5	6	7	8	9	10	11	13	14	15	19	16	17	18	20	21	22
δ^{TMS}_{ppm}	178.7	70.8	139.3	124.8	127.6	125.5	120.6	155.7	39.5	53.4	54.0	30.2	25.2	23.7	46.2	46.8	32.2	19.7	36.0	27.4
Multiplicity	d	s	s	d	d	d	d	s	t	d	s	d	t	t	d	s	t	qa	qa	qa

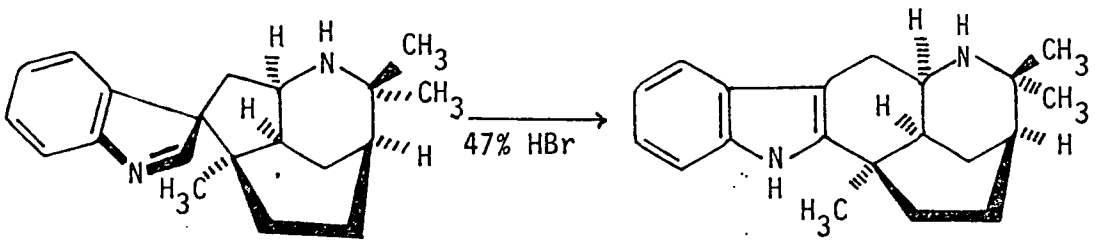
been established by a series of decoupling experiments. The chemical shifts, multiplicities and coupling constants, are summarised in Table VII.



X

The methine proton on carbon C_{11}, α- to the aliphatic nitrogen, appears at 3.83 ppm and is coupled to three neighbouring protons, two of which, at 2.37 (H_{exo}-C_{10}) and 1.87 ppm (H_{endo}-C_{10}), show a large geminal coupling (14.7 Hz) and constitute a methylene group. The third proton (H-C_{16}) resonates at 2.02 ppm and shows coupling (J = 2.5 Hz) with two more protons in a methylene group ($H_{a,b}$-C_{15}), each of which is again coupled to another methine proton (J = 2.5 Hz) on C-14; this in turn is coupled to a pair of geminal protons centred at 1.99 (H_{endo}-C_{19}) and 1.61 (H_{exo}-C_{19}) ppm. The proton at 1.61 also shows a *trans*-vicinal coupling (J = 14.0 Hz) with the H_{endo}-C_{18} proton at 3.16 ppm. The latter is geminally coupled with the other C_{18} proton (H_{exo}-) at 1.00 ppm (J = 14.0 Hz). The P.M.R. spectrum also shows three C-methyl singlets at 1.22, 1.17, and 0.66 ppm. The mass spectra of both aristoteline and aristoserratenine are very similar.

The spectroscopic evidence so far can be accounted for by the structure X for aristoserratenine, which is supported by the ^{13}C-data presented in Table VIII. The presence of this skeleton has been proved by acid-catalysed rearrangement of aristoserratenine into aristoteline in 47% yield. This rearrangement again shows that the



X II

aliphatic parts of both aristoteline and aristoserratenine have the same stereochemistry.

Finally, the absolute stereochemistry around the spiro-carbon has been established by nuclear Overhauser effect experiments. Irradiation of the H_{endo}-C_{18} proton showed a negative enhancement[15] of the C_2-H signal and *vice-versa*.

7. Aristomakine

Aristomakine, isolated in 0.0008% yield from dry plant material, has $[\alpha]_D^{22}$ -79.1° ($CHCl_3$). The molecular formula, $C_{20}H_{26}N_2$, which was determined by high-resolution mass spectrometry shows it is isomeric with aristoteline. However, from its P.M.R. spectrum, aristomakine has two olefinic protons (at 6.02 and 5.72 ppm), and thus it has one less ring than aristoteline. The ultraviolet absorption spectrum (Figure 15) shows the presence of an indole nucleus, and a negative Ehrlich test indicates that both 2- and 3-positions are substituted, which is confirmed by both ^{13}C and P.M.R. spectra. The P.M.R. spectrum shows two broad signals (exchangeable with D_2O) for the indolic N-H and the aliphatic N-H. The ^{13}C N.M.R. spectrum of aristomakine contains two methine carbons at 51.5 and 46.6 ppm which can be assigned to two carbons located α with respect to the non-indolic

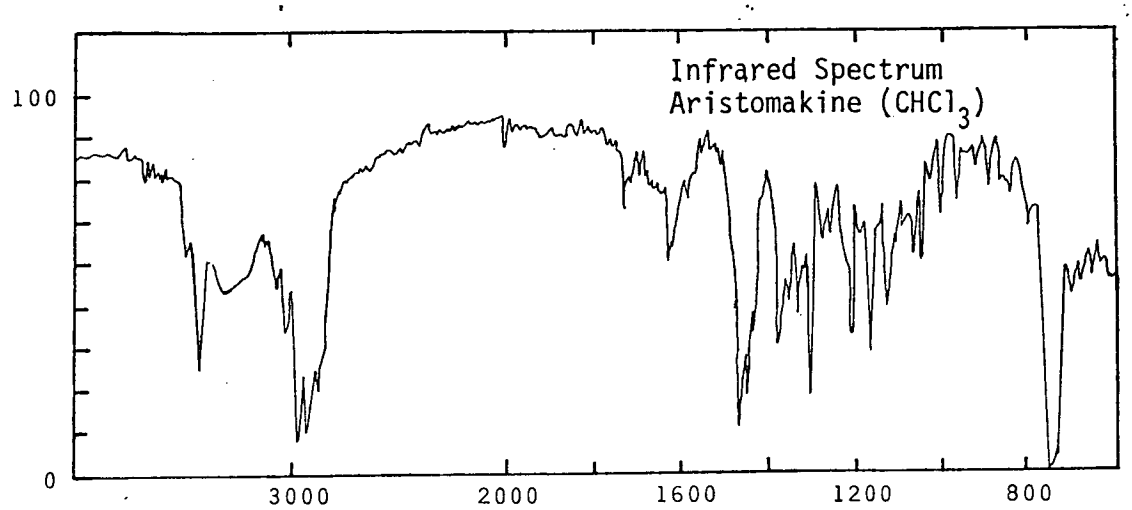


Figure 14.

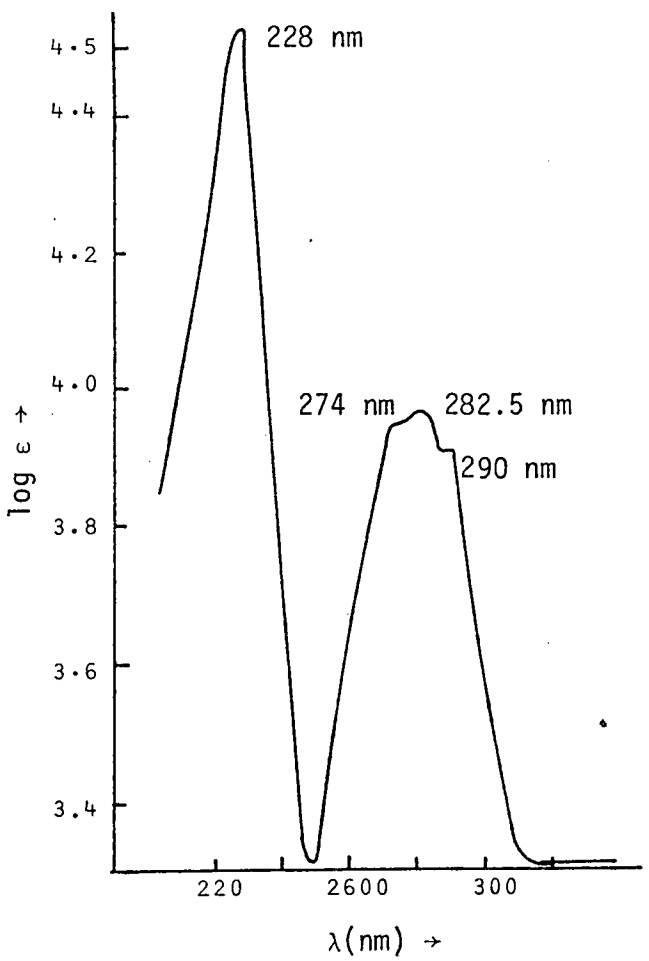
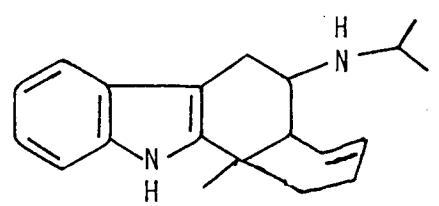


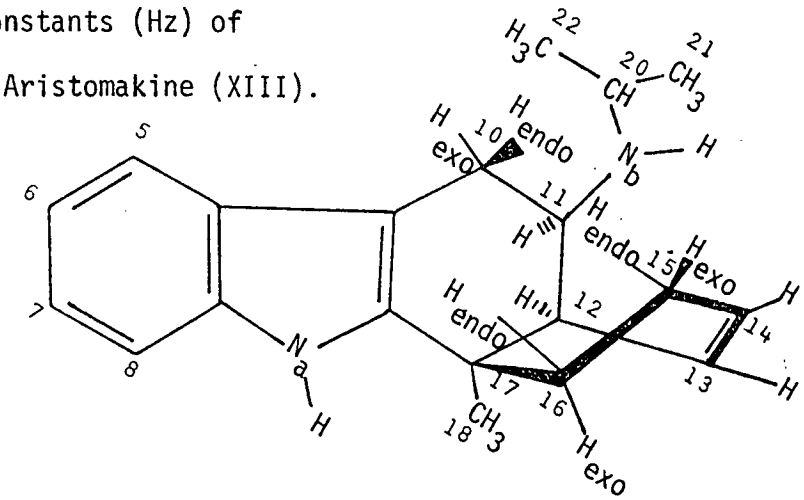
Figure 15.

Ultraviolet Spectrum



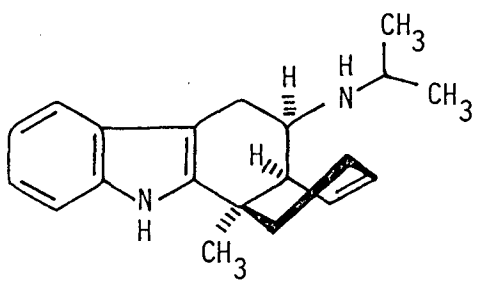
XIII

Table IX. Chemical shifts (ppm), multiplicities, and coupling constants (Hz) of aliphatic and olefinic protons in the pmr spectrum of Aristomakine (XIII).



Protons	H_{endo}-C(10)	H_{exo}-C(10)	H-C(11)	H-C(12)	H-C(13)	H-C(14)	H_{endo}-C(15)	H_{exo}-C(15)	H_{endo}-C(16)	H_{exo}-C(16)	Multiplicities	Chemical shifts
H_{endo}-C(10)		14.8	11.0								dxd	2.30
H_{exo}-C(10)	14.8		5.0								dxd	2.90
H-C(11)	11.0	5.0		3.5							dxdxd	3.44
H-C(12)			3.5			1.5					dxd	2.52
H-C(13)						10.0	1.0	1.0			dxt	6.02
H-C(14)				1.5	10.0		3.0	5.0			dxdxdxd	5.72
H_{endo}-C(15)					1.0	3.0		11.0	2.5	11.0	txdxdxd	1.79
H_{exo}-C(15)					1.0	5.0	11.0		2.5	2.5	dxdxtxd	2.04
H_{endo}-C(16)							2.5	2.5		16.0	dxt	1.86
H_{exo}-C(16)							11.0	2.5	16.0		dxdxd	1.63

nitrogen. Of the two protons attached to these methine carbons, one ($H\text{-}C_{20}$) produces a septet at 3.10 ppm in the P.M.R. spectrum, and is coupled to two sets of geminal methyl protons. Moreover, introduction of an isopropyl group to the non-indolic nitrogen of aristomakinine (XIX) gave aristomakine. Thus, aristomakine has an N-isopropyl group. The other proton, resonating at 3.44 ppm ($H\text{-}C_{11}$) is coupled to two geminal protons ($2H\text{-}C_{10}$) which, from their chemical shifts (2.90 and 2.30 ppm) can be attributed to a methylene group attached to C-3 of the indole nucleus.



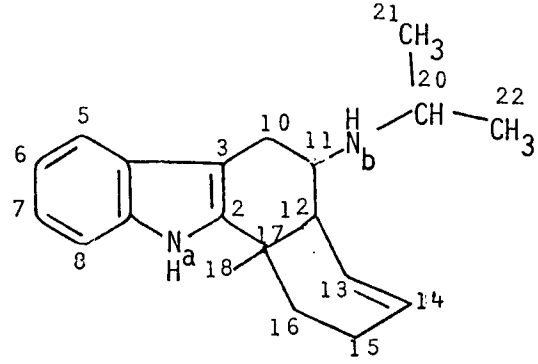
XIII

The sequence of the remaining protons has been established by a series of decoupling experiments. The chemical shifts, multiplicities and coupling constants of these protons are presented in Table IX.

The methine proton at 3.44 ppm ($H\text{-}C_{11}$) is also coupled to another methine proton, (J = 3.5 Hz) resonating at 2.52 ppm ($H\text{-}C_{12}$) which in turn shows an allylic coupling (1.5 Hz) with one of the olefinic protons at 5.72 ppm ($H\text{-}C_{14}$). This olefinic proton is also coupled to a pair of geminal protons at 1.79 ($H_{endo}\text{-}C_{15}$) and 2.04 ($H_{exo}\text{-}C_{15}$) ppm which are further coupled to another pair of geminal protons centred at 1.63 ($H_{endo}\text{-}C_{16}$) and 1.86 ppm ($H_{exo}\text{-}C_{16}$). There is a small allylic coupling (J = 1.0 Hz) between each of the former pair of geminal protons ($2H\text{-}C_{15}$) and the second olefinic proton resonating at 6.02 ppm ($H\text{-}C_{13}$).

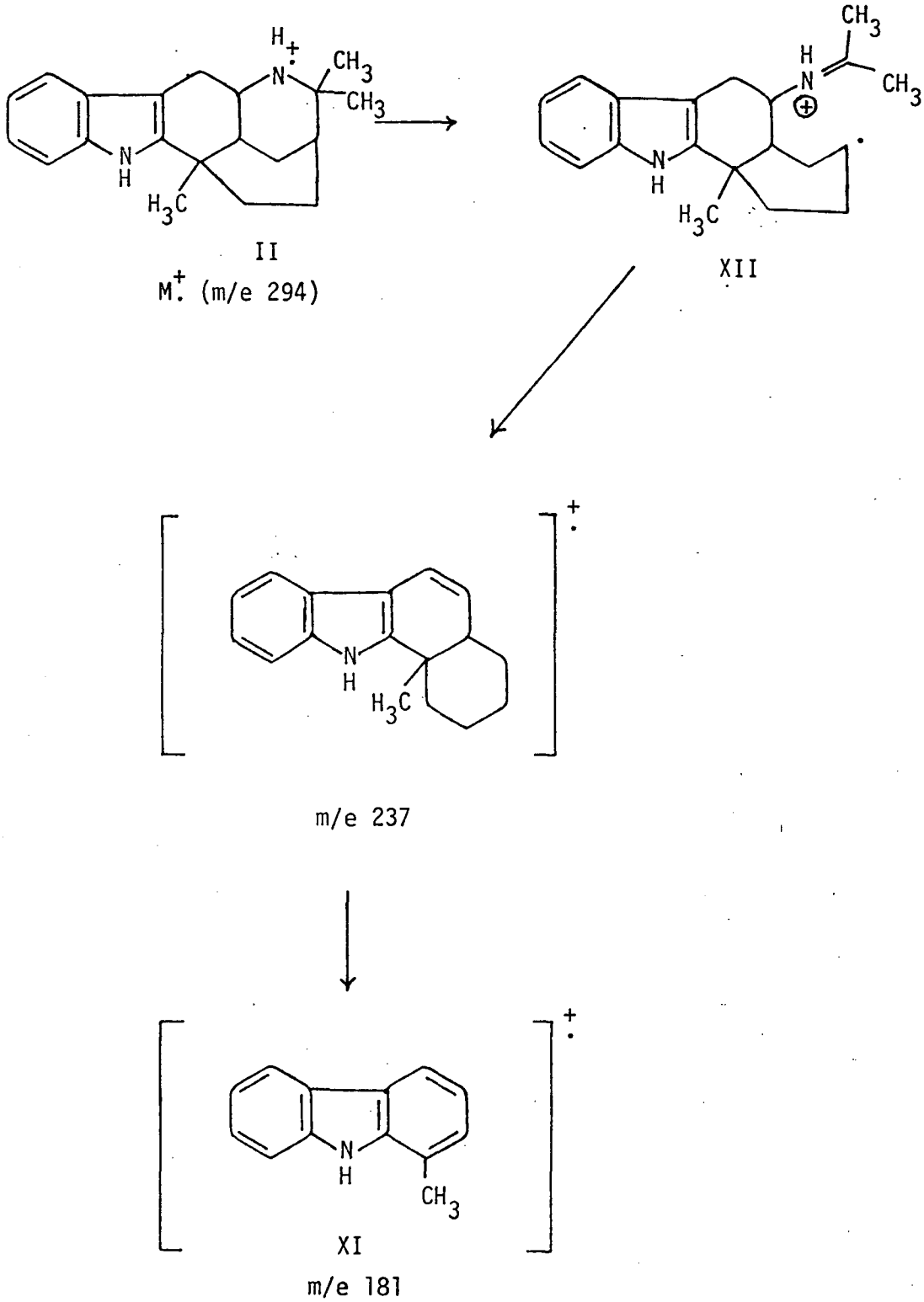
Table X

C-13 Chemical shifts of Aristomakine (measured in $CDCl_3$)

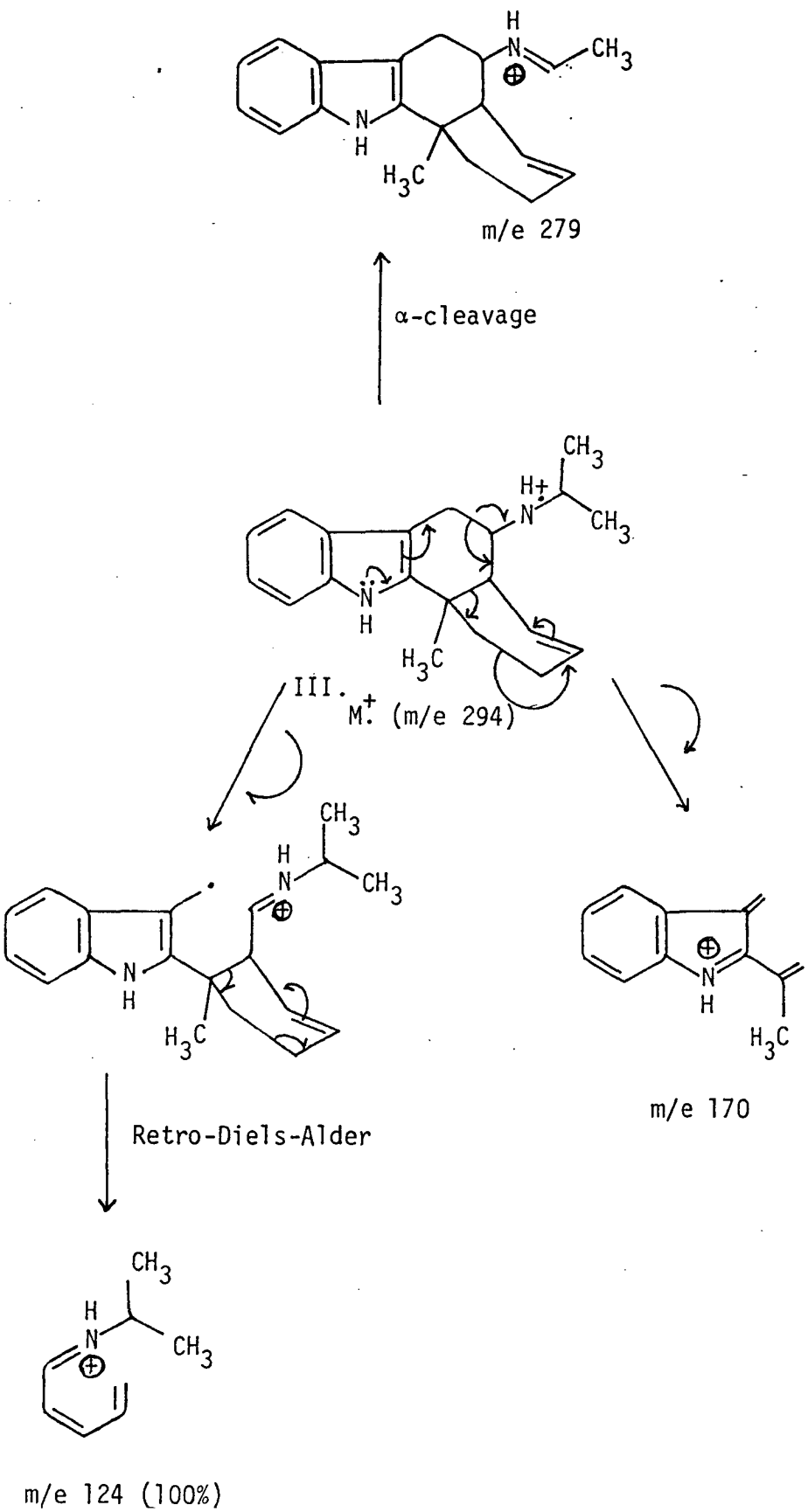


Carbon	2	3	4	5	6	7	8	9	10	16	11	12	13	14	15	17	18	20	21	22
δ^{TMS}_{ppm}	136.3	108.3	127.2	118.1	121.3	119.3	110.6	137.6	24.7	22.7	51.5	44.7	129.8	123.1	34.7	35.4	29.9	46.6	22.3	21.8
Multiplicity	s	s	s	d	d	d	d	s	t	t	d	d	d	d	t	s	qa	d	qa	qa

Scheme 5



Scheme 6


m/e 279
α-cleavage
III.
M.+ (m/e 294)
Retro-Diels-Alder
m/e 170
m/e 124 (100%)

The proton at 1.86 ppm (H_{exo}-C_{16}) shows a large *trans*-diaxial coupling (11.0 Hz) with the proton which appears at 1.79 (H_{endo}-C_{15}) ppm.

The only aliphatic quaternary carbon must in consequence bear the methyl group producing a 3-proton singlet at 1.36 ppm and it is presumably joined at the 2-position of the indole nucleus. This conclusion is supported by the close correspondence in resonance of the C-2 carbon of aristoteline and aristomakine (136.3 and 135.9 ppm respectively) suggesting that these carbons carry similar substituents. This inference is further supported by a series of strong ions between m/e 180 and 183 in the mass spectra of both aristoteline and aristomakine. The m/e 181 fragment from aristoteline has been formulated as XI, and is considered to arise from the ion radical XII (Scheme 5). These observations suggest a structure such as XIII for aristomakine.

All the carbons in the ^{13}C N.M.R. spectrum can be accounted for by this structure. The chemical shifts, multiplicities and assignments are presented in Table X. The mass spectral fragmentations (Scheme 6) are also consistent with structure XIII.

8. Serratoline

Another minor base, serratoline, crystallises from methanol as colourless rhombs, m.p. 157-160°C, $[\alpha]_D^{19}$ - 64.25° ($CHCl_3$). The molecular formula $C_{20}H_{26}N_2O$ has been established by high-resolution mass spectrometry and is supported by elemental analysis. The ultraviolet absorption spectrum (Figure 17) shows that serratoline has an indolenine ring present. The oxygen is present as a hydroxyl group from the infrared (Figure 16) and mass spectra.

On reduction with sodium borohydride, serratoline gave a dihydro-product (XVII), the P.M.R. and ultraviolet spectra of which showed it

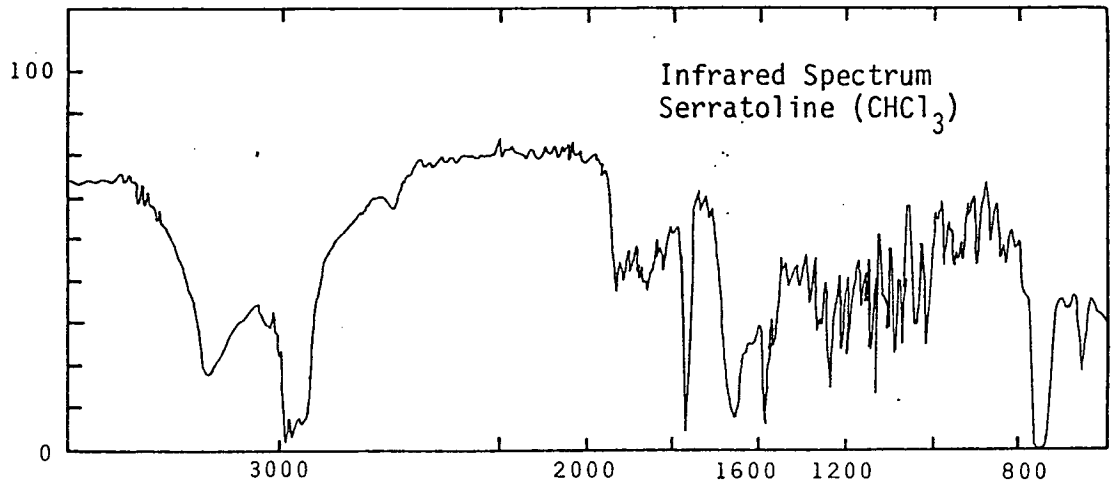


Figure 16.

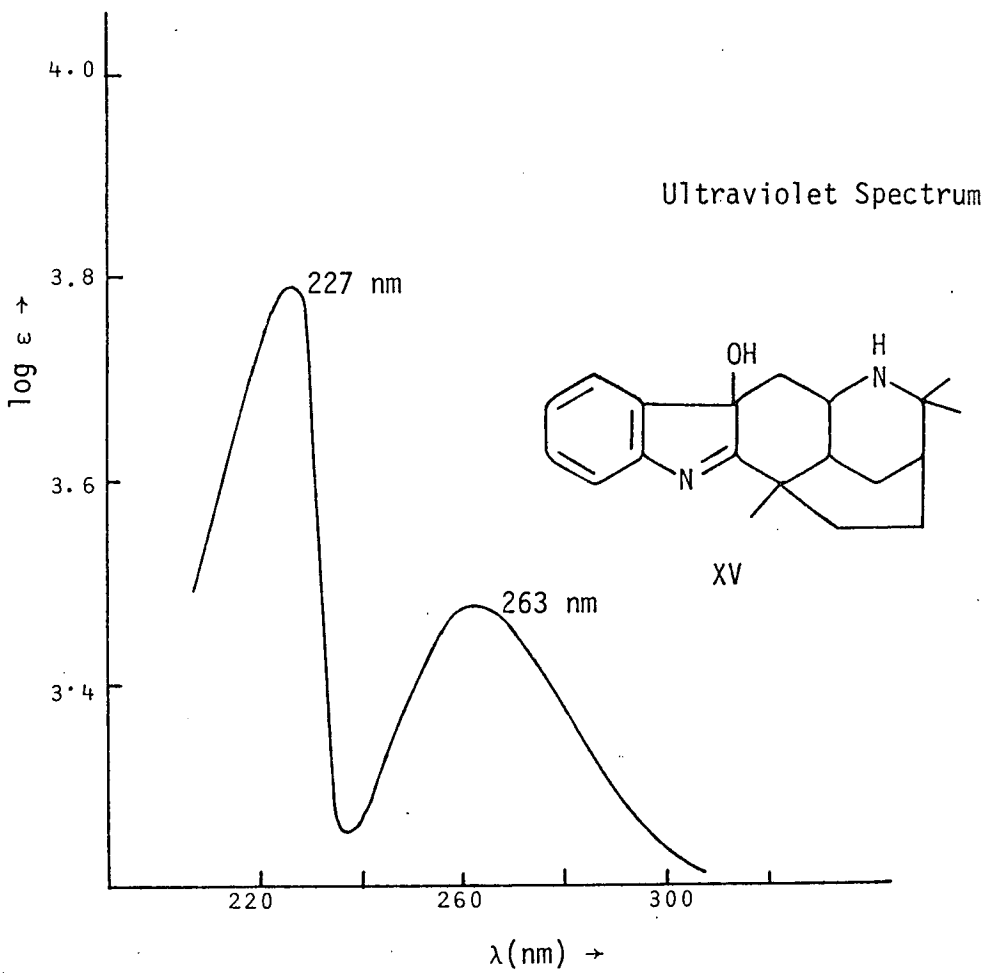
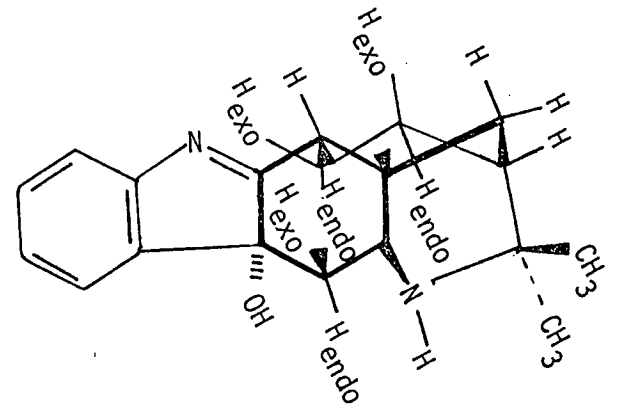


Figure 17.

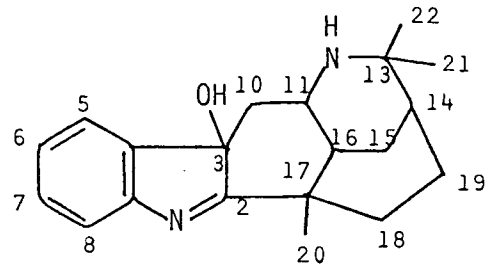
Table XI. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic protons in the pmr spectrum of Serratoline (XV).



Protons	H_{endo}-C(10)	H_{exo}-C(10)	H-C(11)	H-C(16)	2H-C(15)	H-C(14)	H_{endo}-C(19)	H_{exo}-C(19)	H_{endo}-C(18)	H_{exo}-C(18)	Multiplicities	Chemical shifts
H_{endo}-C(10)		14.25	2.9								dxd	1.50
H_{exo} -C(10)	14.25		2.9								dxd	2.45
H-C(11)	2.9	2.9		2.9							qa	3.57
H-C(16)			2.9									
2H-C(15)												
H-C(14)								5.5				
H_{endo}-C(19)								14.0	6.0			
H_{exo} -C(19)						5.5	14.0		14.0	5.5	txt	1.77
H_{endo}-C(18)							6.0	14.0		14.0	txd	3.06
H_{exo} -C(18)								5.5	14.0		dxd	1.37

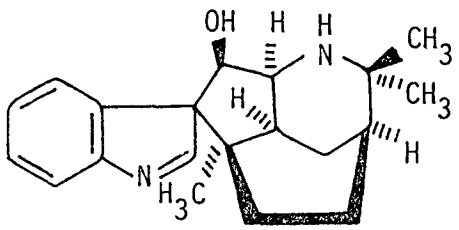
Table XII

^{13}C Chemical shifts of Serratoline (measured in $CDCl_3$)

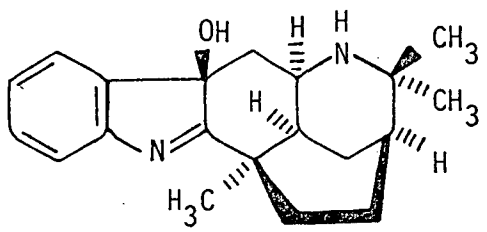


Carbon	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-13	C-14	C-15	C-18	C-19	C-16	C-17	C-20	C-21	C-22
Chemical shifts	189.0	83.9	141.1	121.1	129.1	125.7	120.5	152.6	43.4	52.4	53.6	35.6	26.4	28.3	24.4	44.2	41.5	23.6	29.6	27.9
Multiplicities	s	s	s	d	d	d	d	s	t	d	s	d	t	t	t	d	s	qa	qa	qa

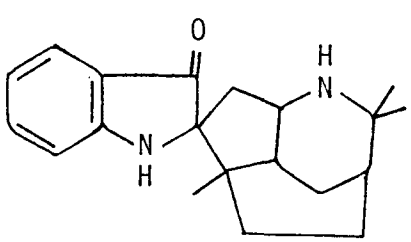
to be an indoline derivative. This substance, when refluxed in dilute acid, lost a molecule of water and gave an indole base which proved identical to the naturally-occurring aristoteline. That the hydroxyl group was not at the 3-position was assumed from its resistance to rearrangement when refluxed in presence of alkali. Structure XIV was eventually assigned to serratoline on the basis of the similarity of its P.M.R. spectrum with that of dihydroaristotelinone (VI), and a possible pathway for the conversion of serratoline to aristoteline was put forward.[12]



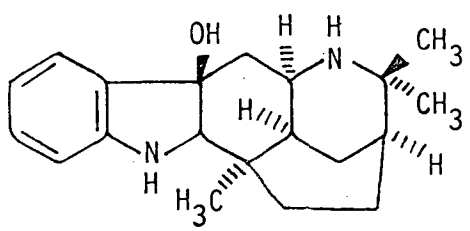
XIV



XV



XVI



XVII

The structure (XIV) has now been revised to (XV) on the basis of the ^{13}C N.M.R. spectrum of serratoline and a number of decoupling experiments on its P.M.R. spectrum.

The ^{13}C N.M.R. spectra of serratoline and aristoserratenine (X) are very similar, except that the former contains only four doublets in the aromatic region instead of five in the latter case. Serratoline also contains an extra quaternary carbon at 189.0 ppm in its ^{13}C N.M.R. spectrum compared to aristoserratenine. This value fits quite well if it is assigned to position 2 of serratoline. A singlet at 7.30 ppm

in the P.M.R. spectrum of serratoline reported[12] earlier must be due to an impurity present in the sample.

The C-3 quaternary carbon in the ^{13}C N.M.R. spectrum of serratoline appears further downfield (at 83.9 ppm) compared to 70.8 ppm in the case of aristoserratenine which suggests that the 3-position of serratoline possibly bears the hydroxyl group. This is supported by the fact that on refluxing in 5% H_2SO_4, serratoline rearranges to a new base which crystallises from methanol as colourless crystals m.p. 217-218°C, $[\alpha]_D$ + 41° ($CHCl_3$). The ultraviolet absorption spectrum of the rearranged product shows that it is a ψ-indoxyl derivative. Its m.p., i.r. spectrum and mass spectral fragmentation proved similar to those of the naturally-occurring aristotelone (XVI).[10] However, a direct comparison has not been possible for lack of an authentic sample of aristotelone.

The aliphatic nitrogen is secondary and is evidently present in the part structure $-CH_2-\underset{|}{CH}-NH-\underset{|}{C}(Me)_2$. The methine carbon ($C-_{11}$) appears at 52.4 ppm in the ^{13}C N.M.R. spectrum of serratoline. The proton on this carbon which appears at 3.57 ppm, is equally coupled to the methylene protons resonating at 2.45 ($H_{exo}-C_{10}$, $J_{11/10exo}$ = 2.9 Hz) and 1.50 ppm ($H_{endo}-C_{10}$, $J_{11/10endo}$ = 2.9 Hz). The methine proton ($H-C_{11}$) is also coupled to another methine proton on $C-_{16}$ with a signal around 1.98 ppm ($J_{11/16}$ = 2.9 Hz). Another low-field aliphatic proton ($H_{endo}-C_{18}$) resonating at 3.06 ppm appears as a doublet of a triplet, and shows a geminal coupling (J_{gem} = 14.0 Hz) with the proton ($H_{exo}-C_{18}$) at 1.37 ppm. Each of the geminal protons is coupled to another pair of methylene protons appearing at 1.73 ($H_{exo}-C_{19}$) and 1.52 ppm ($H_{endo}-C_{19}$) which in turn are coupled to a methine proton at around 1.52 ppm ($H-C_{14}$). The protons $H_{endo}-C_{18}$ and $H_{exo}-C_{19}$ also show a large *trans*-vicinal coupling (J = 14.0 Hz). The P.M.R. spectrum of

serratoline shows three C-methyl singlets.

The chemical shifts, multiplicities and coupling constants of the aliphatic protons are presented in Table XI.

The ^{13}C spectral data presented in Table XII are in full accord with structure XV for serratoline.

Finally, oxidation of aristoteline with benzoyl peroxide to a hydroperoxide and subsequent reduction with sodium dithionite afforded a base which has proved identical to naturally-occurring serratoline (XV). This indicates the absolute stereochemistry of serratoline around all the asymmetric centres except position 3. The configuration at this position can be established from the couplings between the $H\text{-}C_{11}$ proton and the adjacent methylene protons on C-10. From molecular models it is clear that in the particular configuration of C-3 shown in structure XV, the coupling constants between the methine proton ($H\text{-}C_{11}$) and each of the C-10 protons should be the same; whereas the opposite configuration should show a considerable difference between the two coupling constants. The identical coupling constants found experimentally (2.9 Hz) thus establishes the absolute stereochemistry of serratoline as shown in Structure XV.

9. Isohobartine

Isohobartine, also isolated from *Aristotelia fruticosa*, has a molecular formula $C_{20}H_{26}N_2$, established by high-resolution mass spectrometry. The ultraviolet absorption spectrum (Figure 19) shows that it has an indole nucleus present. Isohobartine gives a positive Ehrlich test.

The singlet at 7.03 ppm ($H\text{-}C_{2'}$) in the P.M.R. spectrum of isohobartine, together with a strong m/e 130 peak in its mass spectrum[9] indicates that it is the 2'-position of the indole nucleus which is

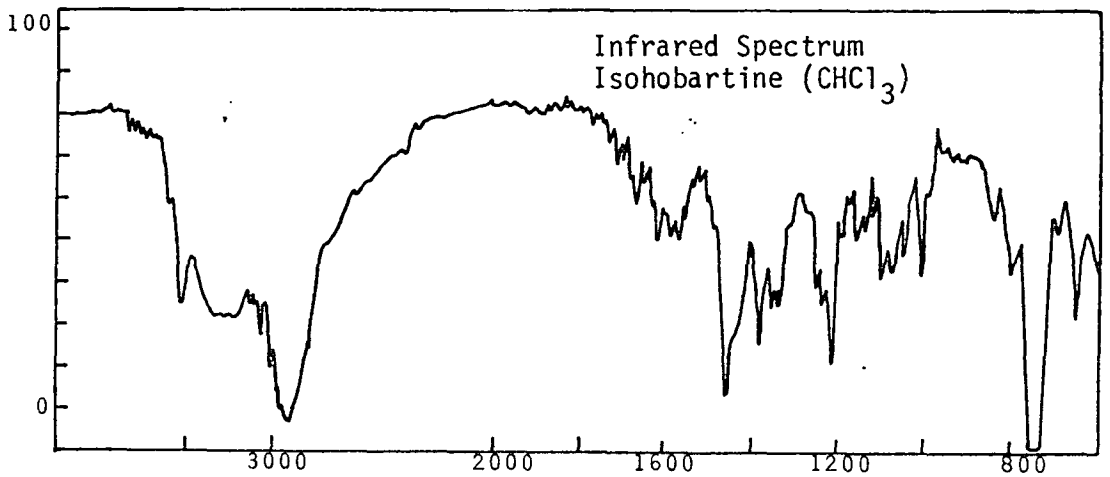
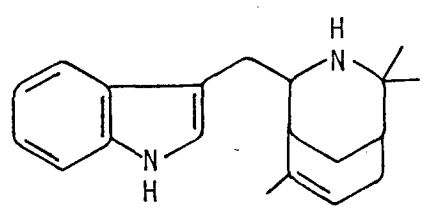


Figure 18.

Ultraviolet Spectrum



XVIII

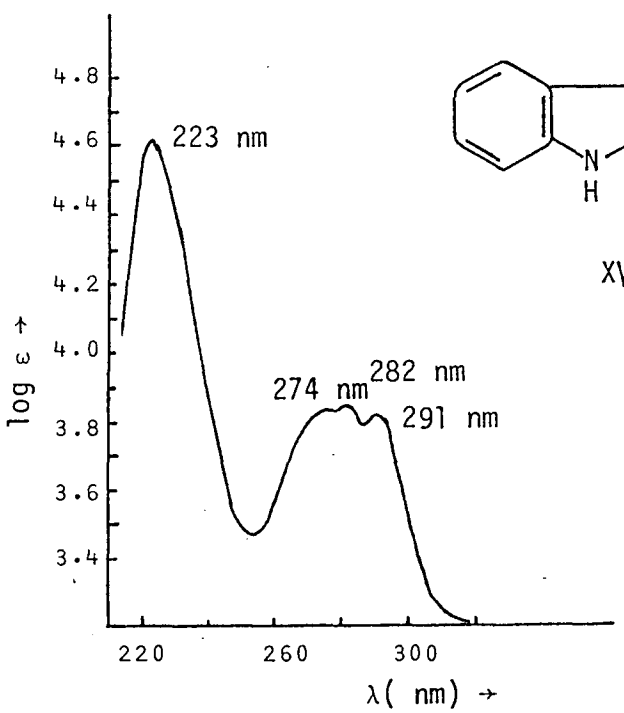
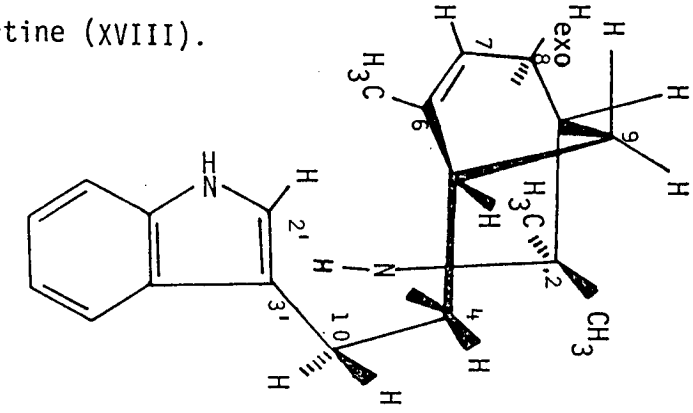


Figure 19.

Table XIII. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic and olefinic protons in the pmr spectrum of Isohobartine (XVIII).



Protons	$H_{a,b}$-C(10)	H-C(4)	H-C(5)	H_a-C(9)	H_b-C(9)	H-C(1)	H_{endo}-C(8)	H_{exo}-C(8)	H-C(7)	3H-C(11)	Multiplicities	Chemical shifts
$H_{a,b}$-C(10)		7.0									d	2.85
H-C(4)	7.0		2.7								txd	3.55
H-C(5)											m	2.20
H_a-C(9)					13.0						dxm	2.10
H_b-C(9)			3.3	13.0		3.3					dxt	1.62
H-C(1)								19.0			m	1.49
H_{endo}-C(8)											dxm	2.32
H_{exo}-C(8)							19.0				dxm	2.05
H-C(7)			1.8				1.8	1.8		1.8	Septet	5.65
3H-C(11)									1.8		d	1.81

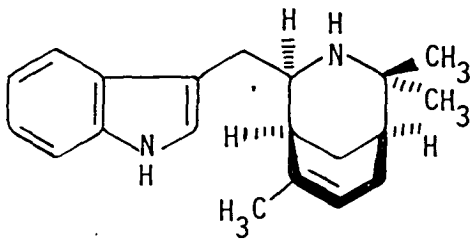
unsubstituted. The P.M.R. spectrum shows the presence of one olefinic proton only, which appears at 5.65 ppm as a septet. It is coupled to the protons of a methyl group ($3H\text{-}C_{11}$), whose signal appears as a doublet (J = 1.8 Hz) at 1.81 ppm. The presence of other prominent peaks at m/e 164 (base peak), 199 and 159 in the mass spectrum indicates moreover that isohobartine has the same skeleton as hobartine.[9] Insufficient amount of the latter was available for a rigid comparison of the two bases; however, isohobartine crystallises from chloroform, on chilling, as colourless crystals, m.p. 134-135°C, $[\alpha]_D^{19}$ - 30 ($CHCl_3$)].* Another observable difference is that, in the P.M.R. spectrum of isohobartine, the methylene protons (H_a, H_b) on C-10 are split by the adjacent methine proton ($H\text{-}C_4$) and appear as a two-proton doublet (J = 7.0 Hz) at 2.85 ppm. On the other hand, in the P.M.R. spectrum of hobartine[9] these methylene protons show a geminal coupling with one another. This difference can be interpreted in terms of a difference in configuration around the C-4 methine carbons.

When isohobartine was treated at room temperature with 47% hydrobromic acid, it gave a rearranged product in 30% yield, identical with the naturally-occurring aristoteline (II). From molecular models it is evident that, of the two possible stereoisomers epimeric at C-4, only XVIII could cyclise under these conditions to aristoteline; and accordingly structure XVIII is assigned to isohobartine. The cyclisation experiment at the same time fixes the absolute stereochemistry of isohobartine.

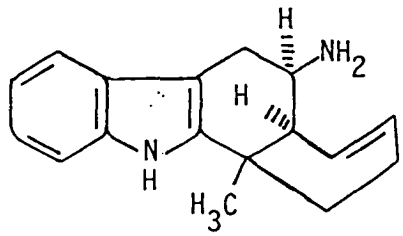
10. Aristomakinine

Aristomakinine, isolated in 0.0004% yield from dry plant material, has $[\alpha]_D^{19}$ - 72° ($CHCl_3$), and the molecular formula $C_{17}H_{20}N_2$, has been

*Reported[9] m.p. for hobartine: 149-150.5° with $[\alpha]_D^{22}$ - 20 ± 3° ($CHCl_3$).



XVIII



XIX

established by high-resolution mass spectrometry. Aristomakinine thus has three carbons less than all the other *Aristotelia* alkaloids so far isolated. The ultraviolet absorption spectrum (Figure 21) shows that it has an indole nucleus present. From the negative test with Ehrlich's reagent, and the absence of any indolic C-2 or C-3 proton signal in the P.M.R. spectrum, it is clear that both these positions of the indole nucleus are substituted.

The proton attached to the indolic nitrogen (H-N_a) appears at 7.96 ppm as a broad singlet, and is exchangeable with D_2O. The addition of D_2O to a sample of the base on the probe of a mass spectrometer resulted in a 3-unit increase in m/e value of the molecular ion peak. Thus aristomakinine must have three replaceable protons altogether; the aliphatic nitrogen evidently bears two protons and is present as a primary amino group. The P.M.R. spectrum of aristomakinine shows the presence of two olefinic protons (H-C_{13} and H-C_{14}) as a singlet at 5.76 ppm and another 3-proton singlet appears at 1.37 ppm ($3H$-C_{18}). There are no signals corresponding to the protons of a geminal dimethyl group or an isopropyl group, as in other *Aristotelia* alkaloids. The mass spectrum shows a strong peak at m/e 170, and a complementary ion peak at m/e 82.

The evidence so far suggests that aristomakinine and aristomakine[13]

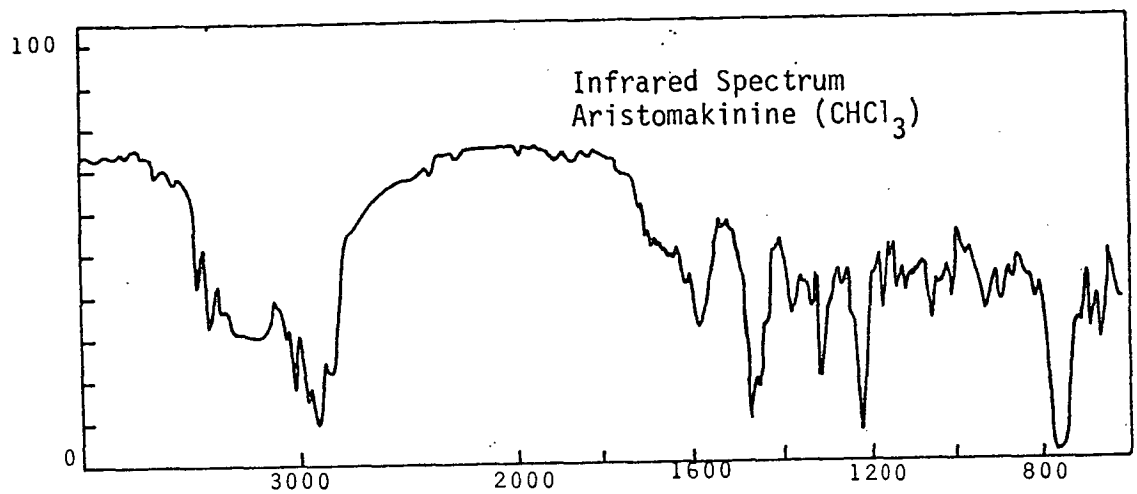
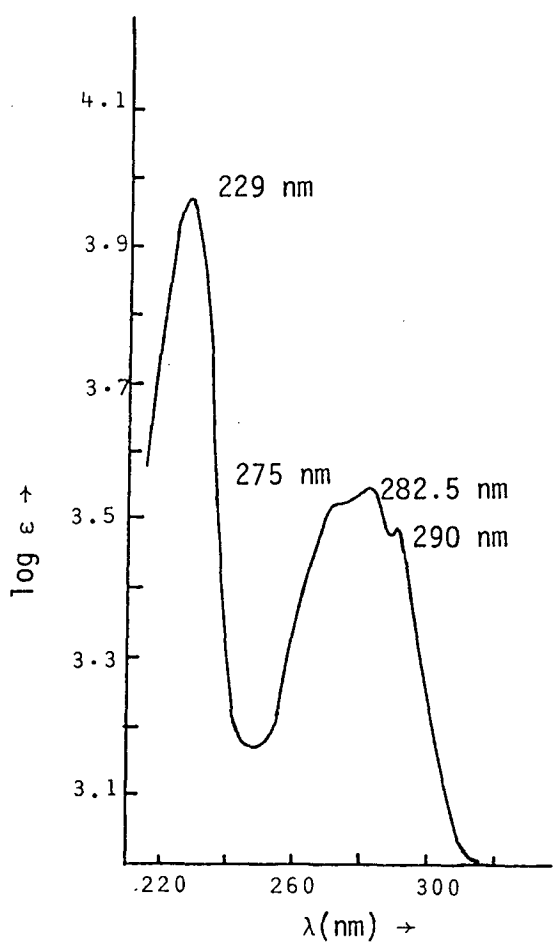
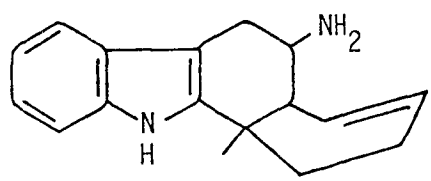


Figure 20.



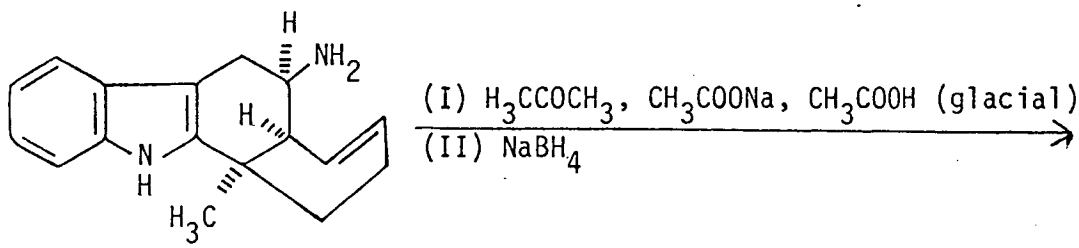
Ultraviolet Spectrum



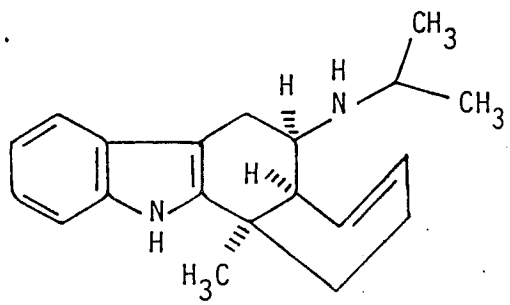
XIX

Figure 21.

(XIII) have similar skeletons, with an isopropyl group missing in the former case. This inference has been proved by the reaction of aristomakinine with acetone followed by reduction with sodium borohydride to give a compound (50% yield) identical with the natural aristomakine (XIII). This experiment establishes the structure and relative stereochemistry of aristomakinine as XIX.



XIX



XIII

11. Isosorelline

Isosorelline, also isolated from *Aristotelia fruticosa*, has a molecular formula $C_{20}H_{24}N_2$, which was established by high-resolution mass spectrometry and confirmed by analysis. The ultraviolet absorption spectrum (Figure 23) shows that it has an indole nucleus present.

The singlet at 6.99 ppm ($H\text{-}C_{2'}$) in the P.M.R. spectrum of isosorelline, together with a strong m/e 130 peak in its mass spectrum, indicates that the 2'-position of the indole nucleus is

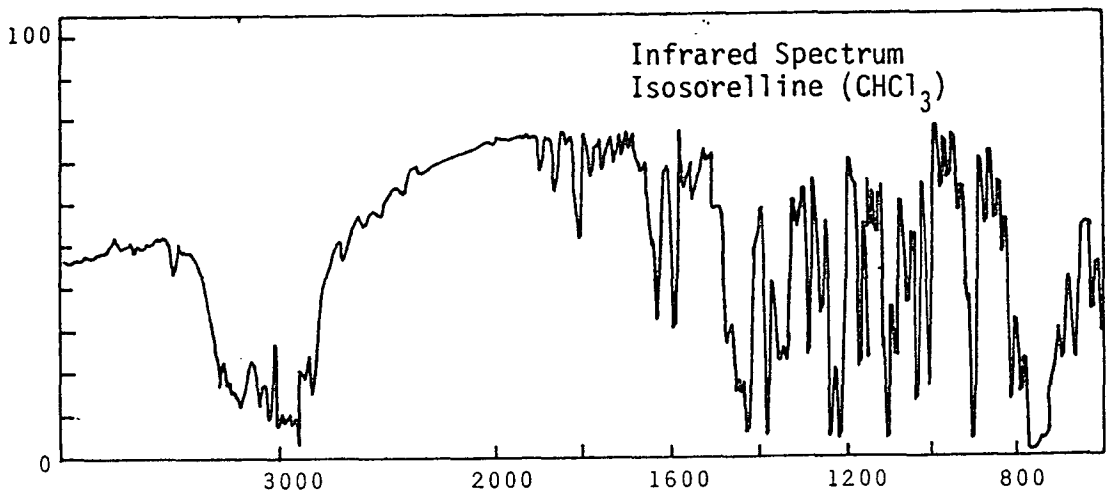
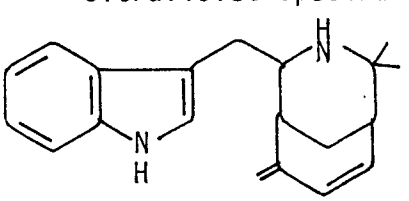


Figure 22.

Ultraviolet Spectrum



XX

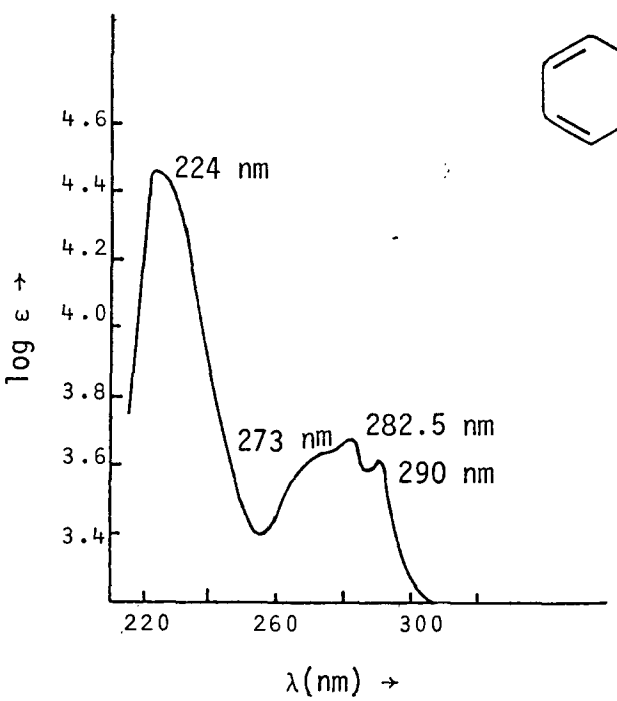
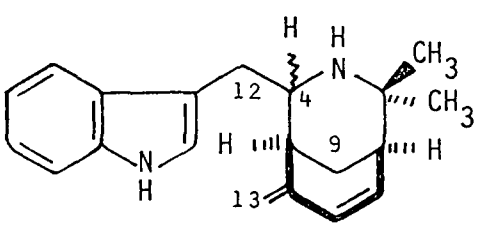


Figure 23.

unsubstituted. This inference has been confirmed by a positive Ehrlich test. The P.M.R. spectrum also shows signals for four olefinic protons, two of which are present in a vinylidine group ($H_{a,b}$-C_{13}). Thus the non-indolic part contains two rings. There is a pair of three-proton singlets (at 1.28 and 1.02 ppm) in the P.M.R. spectrum possibly due to a geminal dimethyl group adjacent to the non-indolic nitrogen, as suggested by the presence of a strong M-15 (m/e 277) peak in the mass spectrum of isosorelline.

The P.M.R. and the mass spectra of sorelline[9] and isosorelline are very similar. However, isosorelline has a m.p. of 160-162°C, $[\alpha]_D^{2.15}$ + 120.7° ($CHCl_3$)[lit.[9] m.p. of sorelline 165-168°C, $[\alpha]_D^{22}$ + 157° ($CHCl_3$)]. They have, moreover, the same R_f values in two different solvent systems. Isosorelline, in its P.M.R. spectrum, has a pair of geminal protons attached to C-12 which, unlike in isohobartine, are geminally coupled.



XX

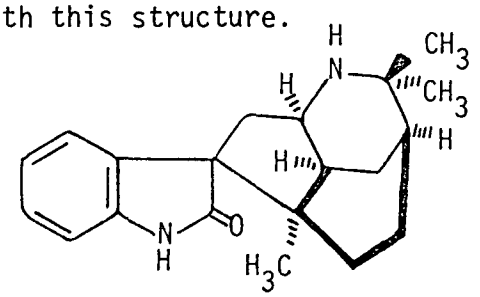
In conformity with the presence of two epimeric alkaloids hobartine-isohobartine, structure (XX) is suggested for isosorelline which possibly has a different configuration around C-4 as compared to sorelline.

12. Tasmanine

Tasmanine has the molecular formula $C_{20}H_{26}N_2O$, as established by high-resolution mass spectrometry. It gives a negative Ehrlich test and crystallises from methanol as colourless crystals, m.p. 249-250°C, $[\alpha]_D^{19}$ - 150° (MeOH). From its molecular formula, tasmanine is isomeric with serratoline (XV). However, the oxygen is present as a carbonyl group as is shown by a strong absorption band at 1700 cm^{-1} in the infrared absorption spectrum of tasmanine (Figure 24). The ultraviolet spectrum (Figure 25) with absorptions at 285, 254 and 217 nm suggests the presence of an oxindole ring.

The P.M.R. spectrum of tasmanine has signals for three C-methyl groups at 1.24, 1.2 and 0.92 ppm. The P.M.R. spectrum also shows two exchangeable proton signals.

On reduction with lithium aluminium hydride, tasmanine gives a major product in 30% yield which has been found to be identical with naturally-occurring aristoteline (II) (Scheme 7). This experiment suggests a structure such as (XXI) for tasmanine and at the same time establishes the stereochemistry around all the chiral centres except the spiro-carbon. The mass spectral fragmentations (Scheme 8) is in accord with this structure.



XXI

Tasmanine has also been isolated from *Aristotelia peduncularis* and the same structure (XXI) has been suggested for it on the basis of spectroscopic data.[14]

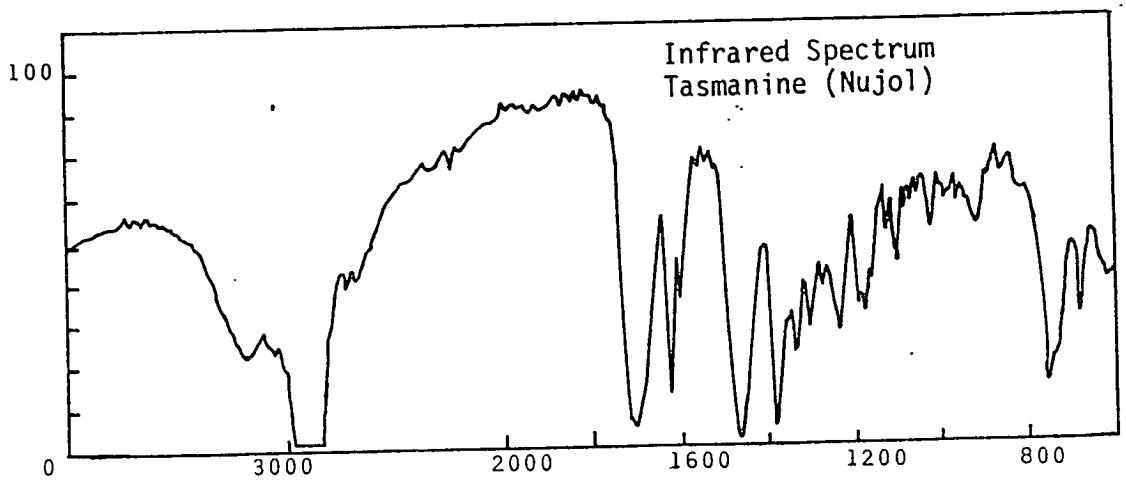
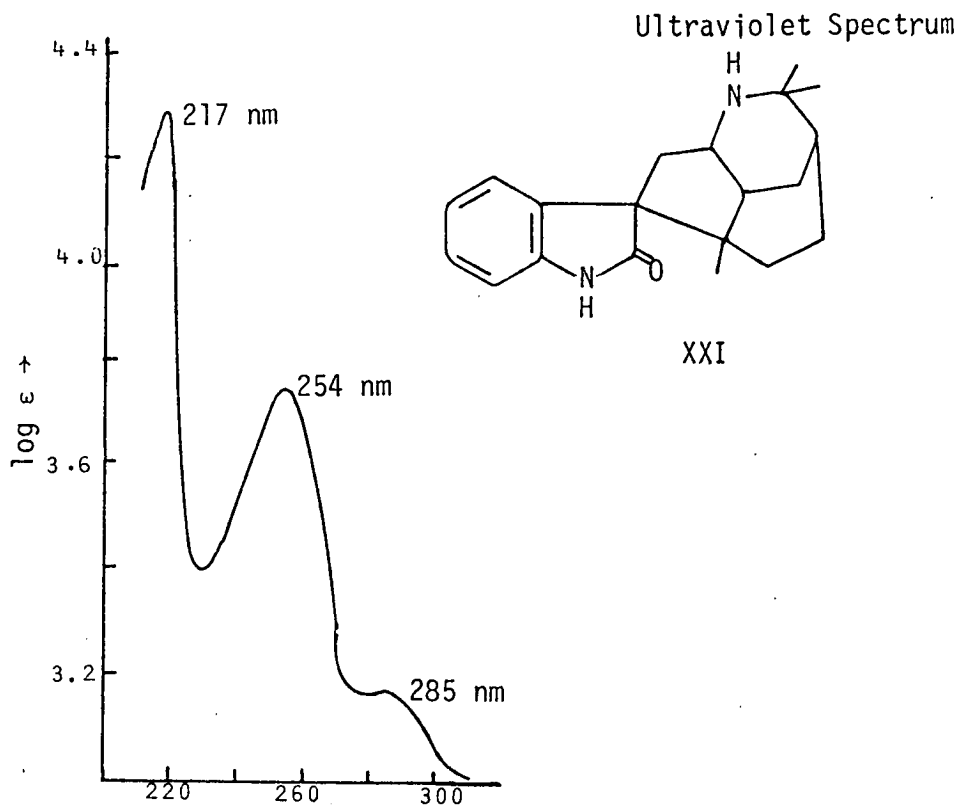
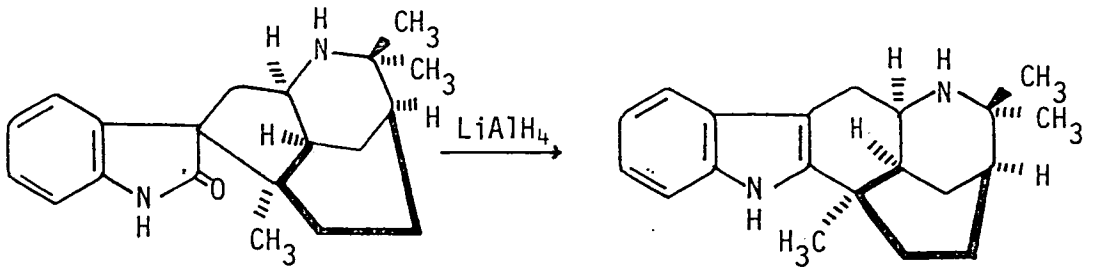


Figure 24.



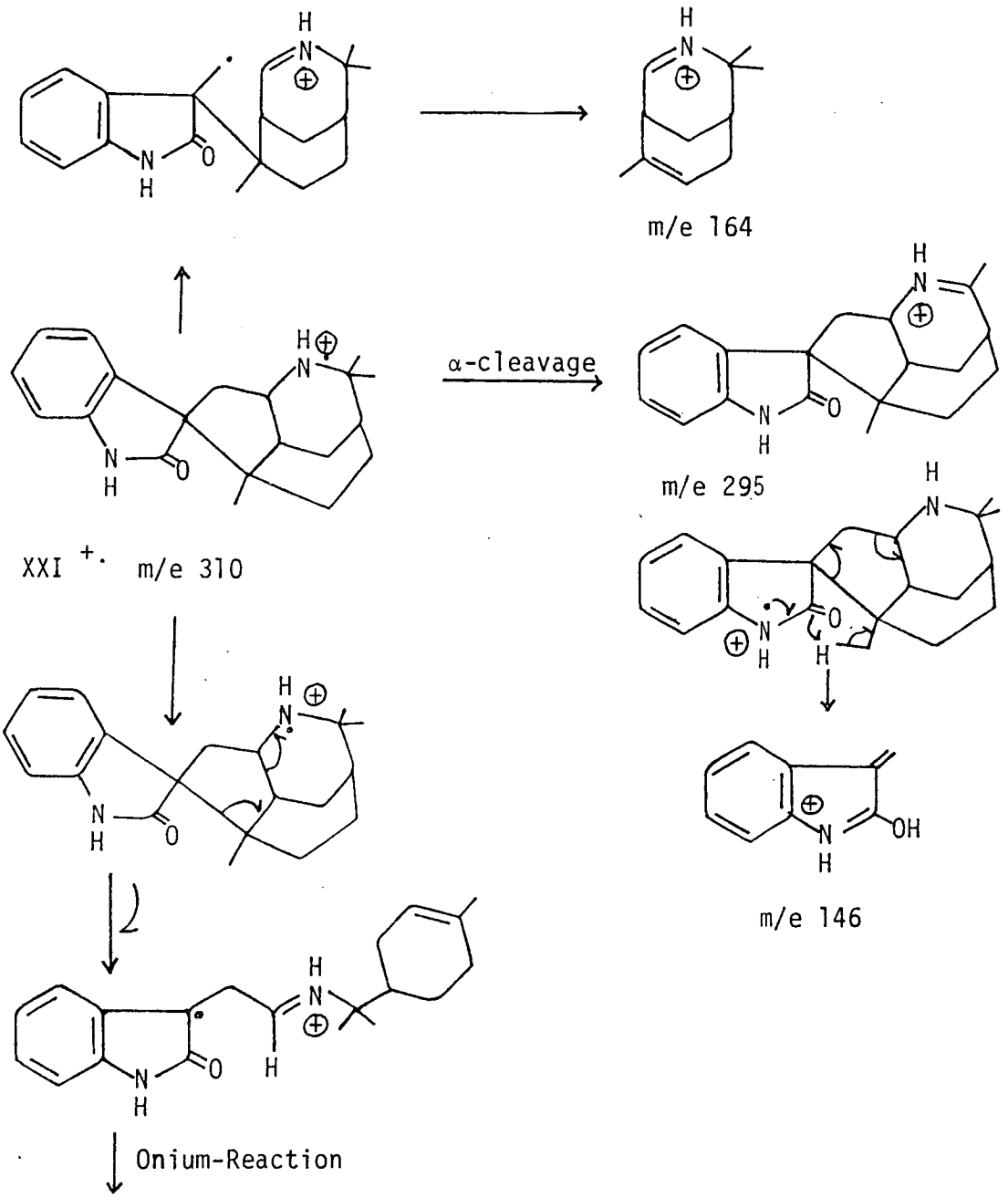
XXI

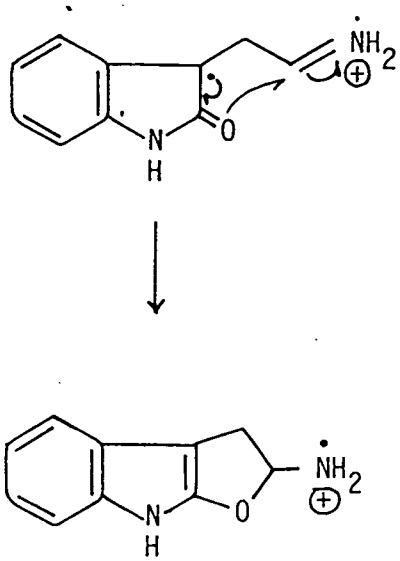
Figure 25.



XXI II

Scheme 7





m/e 174

Scheme 8

2.II. EXPERIMENTAL

Memorandum

Microanalyses were carried out either by the Australian Microanalytical Service, Melbourne, or by Dr. A. Campbell, Chemistry Department, Otago University, Dunedin, New Zealand.

Melting points were determined on a Yanagimoto Seisakusho Micro-Melting Point apparatus and are uncorrected.

Specific optical rotations were measured in solvents (specified in the experimental section) on a "PEPOL 60" Spectropolarimeter.

The 100 MHz proton magnetic resonance (P.M.R.) spectra were recorded with a Jeol JNM-4H-100 MHz spectrometer, and the 270 MHz P.M.R. spectra with a Bruker HX-270 spectrometer. Tetramethylsilane was used as the internal standard. Chemical shifts (δ) are given in p.p.m., coupling constants are in Hertz (Hz). Peaks are described as a singlet (s), doublet (d), triplet (t), quartet (q_a) or as a multiplet (m).

The carbon-13 nuclear magnetic resonance (^{13}C N.M.R.) spectra were determined with a Bruker HX-270 spectrometer operating at 67.89 MHz. Chemical shifts (δ) were measured in p.p.m. from internal tetramethylsilane.

Infrared (I.R.) spectra were recorded on a Beckman IR-33 spectrometer. Absorption bands are described as either strong (s), medium (m) or weak (w) in intensity.

Ultraviolet (U.V.) absorption spectra were recorded on a Hitachi Perkin-Elmer 124 spectrophotometer. Logariths of the extinction coefficients are given in parentheses.

Low resolution mass spectra (M.S.) were run on an EAI Quad 300, employing an inlet temperature of 250° and an electron beam energy

maintained at 70 eV. High resolution mass spectra (H.R.M.S.) were run on an A.E.I. MS 902 spectrometer and on a Vacuum General Micromass 7070 F spectrometer using the direct insertion technique. The source temperature of the latter instrument was 200° and that of the former was 150°. In each instrument the electron beam energy was maintained at 70 eV. Peaks are listed in descending order of m/e ratio.

Thin layer chromatography (t.l.c.) and preparative thin layer chromatography (p.t.l.c.) were performed with Merck silica gel GF_{254} or Camag silica gel DSF-5. In some cases, the silica gel was modified by making up the slurry with 0.5 N potassium hydroxide solution instead of water; this is specified in the Experimental as silica gel - 0.5 N KOH.

Solvents were purified by standard methods. Evaporation of solvents was carried out under reduced pressure.

The general experimental details described above also apply to subsequent experimental sections.

Due to small quantities obtained, elemental analyses on some compounds could not be accomplished. In such cases, high resolution mass spectra were used to determine molecular formulae whenever possible and homogeneity on t.l.c. was used as a criterion of purity.

1. Extraction procedure

Roots, stems and leaves of *Aristotelia serrata* were collected around Rotorua, New Zealand in December, 1977 and were air-dried. The dried plant material was ground to a fine powder (5.5 Kg) in a Wiley mill, and exhaustively extracted with methanol at room temperature

until a test sample gave a negative test with Mayer's reagent. The extract was concentrated *in vacuo* at a temperature below 40°C, to a thick gummy dark brown concentrate which was dissolved in 1 ℓ of warm glacial acetic acid. The solution was poured in a fine stream into 15 ℓ of water whilst rapidly agitating the solution with a vibromixer. The solution was left to stand overnight, and a precipitate that settled out was filtered off, washed with water until free from alkaloids, then discarded. The washings were combined with the acid aqueous solution and evaporated *in vacuo* at a temperature below 35° to dryness. The residue was dissolved in 5 ℓ of water and evaporated again to dryness. The process of dilution with water and evaporation to dryness was repeated once more to get rid of most of the acetic acid. Finally, the residue was dissolved in 3 ℓ of water and the solution was basified to pH 8 with ammonia (d 0.88) whereby a heavy precipitate was formed. Left overnight, the precipitate settled out and was filtered off on a Buchner funnel, dried first under suction, and finally over P_2O_5 under high vacuum at room temperature. The dried precipitate was successively extracted with $CHCl_3$, then 1%, 2%, 5% and finally 10% methanol in $CHCl_3$ until the residue gave a negative Mayer's test. The combined extracts were evaporated *in vacuo* to give 8.60 g of crude alkaloids.

The filtrate was extracted with chloroform (10 x 200 ml). The total chloroform extract was thoroughly extracted with 5% (w/v) sulphuric acid (8 x 150 ml) until free from alkaloids as shown by a negative Mayer's test. The aqueous acid solution was basified with ammonia (d 0.88) and again thoroughly extracted with chloroform (10 x 150 ml). The combined chloroform extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give 3 g of crude alkaloids. When the

crude alkaloid samples were mixed together the total yield obtained was 11.6 g (0.21%).

2. Initial separation procedure

The crude alkaloid mixture (11.6 g) was dissolved in chloroform (80 ml) and introduced into the first two tubes of a Gallenkamp Craig counter-current apparatus coupled to an automatic fraction collector. The machine was programmed to shake for 2½ min after each settling interval of 20 min. The crude alkaloids were subjected to counter-current distribution using chloroform as the stationary phase and 1 x 10^{-3} N sulphuric acid as the mobile phase. About 40 ml of mobile phase was transferred at the end of each interval, and every tenth transfer was monitored by analytical t.l.c. after basification and extraction of an aliquot of the aqueous eluent with chloroform. The fractions were bulked accordingly and the bulking summary is shown in Table I.

Bulked fractions from the counter-current distribution were each individually examined, and the best chromatographic conditions for the separation and purification of their constituent alkaloids were determined; each was then subjected to p.t.l.c.

3. Isolation, purification and characterisation of the alkaloids

Fraction 14

Analytical t.l.c. in a number of different solvent systems showed a single spot, R_f 0.75 (2% MeOH/$CHCl_3$). Crystallisation from methanol afforded colourless crystals of aristoserratine (50 mg), m.p. 112-114°C (solvate), 199°C (after drying for 10 hr

Table I

Bulking Summary of fractions isolated after counter-current distribution

Tube Nos.	Fraction	Wt. of recovered alkaloids (g)
1-40	1	0.90
41-120	2	1.50
121-200	3	1.60
201-280	4	1.30
281-324	5	0.70
325-410	6	1.35
411-445	7	0.50
446-480	8	0.50
481-515	9	0.50
516-545	10	0.40
546-570	11	0.40
571-590	12	0.28
591-650	13	0.23
651-720	14	0.25

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in vacuo). It also crystallised from absolute acetone, m.p. 192-193°C. It had $[\alpha]_D^{19}$ + 22.5° (C = 1.9, chloroform), λ_{max} (EtOH): 228 nm (4.42), 275 nm (sh, 3.79), 282 nm (3.82), 2 90 nm (3.75); ν_{max} ($CHCl_3$): 3473 cm^{-1} (HN), 3330 cm^{-1} (broad, HN), 1710 cm^{-1} (S, C=O); P.M.R. (δ ppm): 8.18 (1H, broad singlet, H-N_a; exchangeable with D_2O); 7.47-7.09 (4H, multiplet, aromatic protons); 3.79 (1H, ddd, $J_{11/10exo}$ = 5.7 Hz, $J_{11/16}$ = 2.5 Hz, $J_{11/10endo}$ = 1.5 Hz, H-C_{11}); 3.08 (1H, dd,

$J_{gem(10exo/10endo)}$ = 16.8 Hz, $J_{10exo/11}$ = 5.7 Hz, H_{exo}-C_{10}); 2.80 (1H, dd, $J_{gem(10endo/10exo)}$ = 16.8 Hz, $J_{10endo/11}$ = 1.5 Hz, H_{endo}-C_{10}); 2.58 (1H, td, $J_{18endo/18exo,19exo}$ = 13.8 Hz, $J_{18endo/19endo}$ = 5.8 Hz, H_{endo}-C_{18}); 2.35 (1H, dd, $J_{16/11}$ = 2.5 Hz, $J_{16/14}$ = 1.3 Hz, H-C_{16}); 2.18 (1H, dddd, $J_{gem(19endo/19exo)}$ = 14.2 Hz, $J_{19endo/18endo}$ = 5.8 Hz, $J_{19endo/14}$ = 2.5 Hz, $J_{19endo/18exo}$ = 2.0 Hz, H_{endo}-C_{19}); 2.08 (1H, ddd, $J_{14/19exo}$ = 3.8 Hz, $J_{14/19endo}$ = 2.5 Hz, $J_{14/16}$ = 1.3 Hz, H-C_{14}); 1.92 (1H, dddd, $J_{gem(19exo/19endo)}$ = 14.2 Hz, $J_{19exo/18endo}$ = 13.8 Hz, $J_{19exo/18exo}$ = 5.6 Hz, $J_{19exo/14}$ = 3.8 Hz, H_{exo}-C_{19}); 1.65 (1H, ddd, $J_{gem(18exo/18endo)}$ = 13.8 Hz, $J_{18exo/19exo}$ = 5.6 Hz, $J_{18exo/19endo}$ = 2.0 Hz, H_{exo}-C_{18}); Ca. 1.5 (1H, br. s, H-N_b; exchangeable with D_2O); 1.38 (3H, s, 3H-C_{20}); 1.19 (6H, s, 3H-C_{21} + 3H-C_{22}). H.R.M.S.: 308 ($M^{+\cdot}$, 67). Meas.: 308.1846; calc. for $C_{20}H_{24}N_2O$: 308.1888; 293 (33, $C_{19}H_{21}N_2O$), 251 (11, $C_{17}H_{17}NO$), 236 (10, $C_{16}H_{14}NO$), 226 (18), 225 (100, $C_{15}H_{15}NO$), 194 (10), 184 (12), 183 (21), 182 (33), 181 (12), 180 (27), 168 (17), 167 (21), 162 (13), 154 (11), 143 (32), 130 (12), 110 (20), 84 (16). Analysis: Found: C, 77.61; H, 7.79; N, 9.25. Calculated for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.01%.

Fraction 13

Analytical t.l.c. (silica gel - 0.5 N KOH: 2.5% MeOH/$CHCl_3$) revealed the presence of one major and one minor component. The mixture was separated by p.t.l.c. (2.5% MeOH/$CHCl_3$). The component of higher R_f proved to be aristoserratine.

The minor component (lower R_f band) was isolated in an amount too small for further studies.

Fraction 12

Analytical t.l.c. (silica gel - 0.5 N KOH: 2.5% MeOH/$CHCl_3$)

showed the presence of at least two alkaloids. The mixture was subjected to p.t.l.c. (2.5% MeOH/$CHCl_3$). From the higher R_f band was isolated a new alkaloid (60 mg), named aristotelinone, which had R_f 0.63 (2.5% MeOH/$CHCl_3$) and gave a negative Ehrlich test. It crystallised from methanol in colourless long fine needles, changing around 255° into longer needles which remained unaltered up to 320°C. It had $[\alpha]_D^{19}$ + 122.7° (MeOH + $CHCl_3$ 1:1), λ_{max} (MeOH): 301 nm (4.02), 266.5 nm (4.07), 245 nm (4.31), 216 nm (4.56); ν_{max} (Nujol): 3250 cm^{-1} (broad, HN), 1610 cm^{-1} (s, unsaturated C=O); ν_{max} ($CHCl_3$ soln.): 1632 cm^{-1} (s); P.M.R. ($CDCl_3$ + $MeOD_4$ 1:1, δ ppm): 8.15 (1H, broad, H-N_a, exchangeable with D_2O); 7.19-7.39 (4H, multiplet, aromatic protons); 3.65 (1H, d, $J_{11/16}$ = 3.1 Hz, H-C_{11}); 2.69 (1H, td, $J_{18endo/18exo,19exo}$) = 13.8 Hz, $J_{18endo/19endo}$ = 5.0 Hz, H_{endo}-C_{18}); 2.06 (1H, qa, $J_{16/11,15_{a,b}}$ = 3.1 Hz, H-C_{16}); 1.97-1.80 (3H, multiplet, H_{endo}-C_{19} + H_a-C_{15} + H_b-C_{15}); 1.75-1.61 (1H, multiplet, H_{exo}-C_{19}); 1.56 (1H, dd, $J_{gem(18exo/18endo)}$ = 13.8 Hz, $J_{18exo/19exo}$ = 5.0 Hz, H_{exo}-C_{18}); 1.55 (3H, s, 3H-C_{20}); 1.48 (1H, multiplet, H-C_{14}); 1.35-1.40 (1H, broad, H-N_b); 1.29 and 1.07 (6H, 2s, 3H-C_{21} + 3H-C_{22}); H.R.M.S.: m/e 308 ($M^{+\cdot}$, 27). Meas.: 308.1855; calc. for $C_{20}H_{24}N_2O$: 308.1888; 294 (20, $C_{19}H_{22}N_2O$); 293 (100, $C_{19}H_{21}N_2O$); 251 (21, $C_{17}H_{17}NO$); 236 (4, $C_{16}H_{14}NO$); 184 (7); 167 (4), 143 (3.5); 84 (3%). Analysis: Found: C, 77.64; H, 7.58; N, 9.0. Calc. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.08%. ^{13}C N.M.R. ($CDCl_3$ + $MeOD_4$ 1:1, δ_{ppm}^{TMS}): 195.5 (s, C-10); 162.6 (s, C-2); 139.0 (s, C-9); 127.0 (s, C-4); 123.5 (d, C-6); 127.7 (d, C-7); 121.8 (d, C-5); 111.9 (d, C-8); 109.0 (s, C-3); 61.0 (d, C-11); 53.3 (s, C-13); 41.4 (d, C-16); 37.0 (d, C-14); 35.5 (s, C-17); 34.4 (t, C-18); 29.4 and 27.3 (2qa, C-21 + C-22); 26.1 and 25.0 (2t, C-15 + C-19); 22.9 (qa, C-20).

The lower R_f band was extracted to give 33 mg of another new alkaloid,

makonine, which gave a negative Ehrlich test. It was crystallised from methanol as hexagonal crystals, m.p. 310-312°C (d), $[\alpha]_D^{19}$ + 431.1° (MeOH + $CHCl_3$ 1:2); λ_{max} (MeOH): 314 nm (4.37), 273 nm (4.46), 255 nm (4.46), 218 nm (4.57); λ_{max} (after addition of a drop of 2.5 N H_2SO_4): 364 nm (4.2), 281 nm (4.43), 273 nm (4.42), 223 nm (4.64); ν_{max} (Nujol): 3250 cm^{-1} (broad, HN), 1645 cm^{-1} (m, C=N), 1610 cm^{-1} (s, conjugated C=O); P.M.R. ($CDCl_3$ + $MeOD_4$, δ ppm): 8.2 (1H, broad, H-N_a, exchangeable with D_2O); 7.1-7.4 (4H, multiplet, aromatic protons); 2.83 (1H, t, $J_{16/15a,b}$ = 2.0 Hz, H-C_{16}); 2.06 (2H, multiplet); 1.7-2.0 (5H, multiplet); 1.7 (3H, s, 3H-C_{20}); 1.35 and 1.32 (6H, 2s, 3H-C_{21} + 3H-C_{22}): H.R.M.S.: m/e 306 (M^+, 90). Meas.: 306.1727; calc. for $C_{20}H_{22}N_2O$: 306.1732, 291 (22), 252 (24), 251 (100), 249 (12), 236 (34), 167 (13%). Analysis: Found: C, 74.20; H, 7.73; N, 8.18. $C_{20}H_{22}N_2O$, CH_3OH requires: C, 74.50; H, 7.74; N, 8.28%. ^{13}C N.M.R. ($CDCl_3$ + $MeOD_4$, δ_{ppm}^{TMS}): 186.2 (s, C-10); 170.5 (s, C-11); 161.5 (s, C-2); 137.2 (s, C-9); 125.0 (s, C-4); 123.9 (d, C-6); 123.0 (d, C-7); 121.6 (d, C-5); 112.1 (d, C-8); 112.0 (s, C-3); 58.6 (s, C-13); 45.7 (d, C-16); 40.5 (s, C-17); 36.3 (d, C-14); 33.3 (t, C-18); 29.9 and 27.0 (2qa, C-21 + C-22); 24.3 and 21.5 (2t, C-15 + C-19); 19.3 (qa, C-20).

The remaining minor components were in very small amounts, insufficient for further studies.

Fraction 11

Attempted crystallisation of the crude fraction afforded crystals of aristotelinone (80 mg). The mother liquor contained three alkaloids, as revealed by analytical t.l.c. (2.5% MeOH/$CHCl_3$) and was subjected to p.t.l.c. (2.5% MeOH/$CHCl_3$, double development). The higher R_f band proved to be aristotelinone.

The middle R_f band was extracted to give 36 mg of a new alkaloid, named serratenone, which gave a positive Ehrlich test. It could not be crystallised, but had $[\alpha]_D^{19}$ - 45° (C 1.0, $CHCl_3$), λ_{max} (MeOH): 290 nm (3.49), 281 nm (3.56), 273 nm (sh, 3.55), 241 nm (sh, 3.88), 223 nm (4.31), 209 nm (sh, 4.09); ν_{max} ($CHCl_3$): 3400 cm^{-1} (HN), 3250-3350 cm^{-1} (broad, HN), 1650 cm^{-1} (s, α,β-unsaturated C=O group); P.M.R. (δ ppm): 8.32 (1H, broad singlet, H-N_a, exchangeable with D_2O); 7.18-7.70 (4H, multiplet, aromatic protons); 7.12 (1H, s, H-$C_{2'}$); 6.06 (1H, quintet, $J_{allylic(7/5,11)}$ = 1.0 Hz, H-C7); 3.75 (1H, ddd, $J_{4/10b}$ = 7.50 Hz, $J_{4/10a}$ = 6.0 Hz, $J_{4/5}$ = 2.4 Hz, H-C_4); 2.93 (1H, dd, $J_{gem(10a/10b)}$ = 13.5 Hz, $J_{10a/4}$ = 6.0 Hz, H_a-C_{10}); 2.65 (1H, dd, $J_{gem(10b/10a)}$ = 13.5 Hz, $J_{10b/4}$ = 7.5 Hz, H_b-C_{10}); 2.48 (1H, qad, $J_{5/4,9a,9b}$ = 2.4 Hz, $J_{allylic(5/7)}$ = 1.0 Hz, H-C_5); 2.25 (2H, t, $J_{9/5,1}$ = 2.4 Hz, 2H-C_9); 2.08 (3H, d, $J_{allylic(11/7)}$ = 1.0 Hz, 3H-C_{11}); 2.00 (1H, t, $J_{1/9a,9b}$ = 2.4 Hz, H-C_1); 1.82 (1H, broad, H-N_b, disappears on addition of D_2O); 1.18 and 1.06 (6H, 2s, 3H-C_{12} + 3H-C_{13}). H.R.M.S.: m/e 308 ($M^{+\cdot}$, 11). Meas.: 308.1843; calc. for $C_{20}H_{24}N_2O$: 308.1888; 293 (4); 251 (3, $C_{17}H_{17}NO$); 208 (3); 199 (26, $C_{13}H_{15}N_2$); 179 (20); 178 (100%; 159 (26, $C_{10}H_{11}N_2$); 143 (20, $C_{10}H_9N$); 131 (30); 130 (75); 117 (33, C_8H_7N); 110 (30%).

From the lowest R_f band was isolated another new alkaloid (74 mg), which was named makomakine. It gave a positive Ehrlich test and crystallised from chloroform on chilling, as colourless crystals, m.p. 99-100°C, $[\alpha]_D^{19}$ (+) 131.2° (C, 0.50, $CHCl_3$); λ_{max} (MeOH): 291 nm (3.75), 282 nm (3.79), 276 nm (sh, 3.76), 223 nm (4.53); ν_{max} ($CHCl_3$): 3400 cm^{-1} (HN), 3250 cm^{-1} (broad, HN), 1640 cm^{-1} (m, >C=C<); P.M.R. (δ ppm): 8.03 (1H, broad singlet, H-N_a, exchangeable with D_2O); 7.0-7.70 (4H, multiplet, aromatic protons);

6.95 (1H, s, H-$C_{2'}$); 4.78 (1H, dd, $J_{13a/13b}$ = 2.55 Hz, $J_{13a/7endo}$ = 2.45 Hz, H_a-C_{13}); 4.58 (1H, dd, $J_{13b/13a}$ = 2.55 Hz, $J_{13b/7endo}$ = 2.45 Hz, H_b-C_{13}); 3.48 (1H, ddd, $J_{4/10b}$ = 7.6 Hz, $J_{4/10a}$ = 6.0 Hz, $J_{4/5}$ = 2.7 Hz, H-C_4); 3.06 (1H, tdt, $J_{7endo/7exo,8exo}$ = 14.2 Hz, $J_{7endo/8endo}$ = 6.7 Hz, $J_{7endo/13a,13b}$ = 2.45 Hz, H_{endo}-C_7); 2.75 (1H, dd, $J_{gem(10a/10b)}$ = 14.25 Hz, $J_{10a/4}$ = 6.0 Hz, H_a-C_{10}); 2.70 (1H, dd, $J_{gem(10b/10a)}$ = 14.25 Hz, $J_{10b/4}$ = 7.6 Hz, H_b-C_{10}); 2.26 (1H, qa, $J_{5/4,9a,9b}$ = 2.7 Hz, H-C_5); 2.0-2.1 (3H, multiplets); 1.80 (1H, broad, H-N_b, exchangeable with D_2O); 1.57 (1H, dt, $J_{gem(9a/9b)}$ = 12.7 Hz, $J_{9a/5,1}$ = 2.7 Hz, H_a-C_9); 1.40-1.55 (2H, multiplets); 1.13 and 1.10 (6H, 2s, 3H-C_{11} + 3H-C_{12}); H.R.M.S.: m/e 294 (M^+, 48). Meas.: 294.2097; calc. for $C_{20}H_{26}N_2$: 294.2096; 279 (34), 199 (4), 165 (13), 164 (100), 159 (12), 131 (9), 130 (53), 117 (6), 93 (14), 91 (8), 77 (15). ^{13}C N.M.R. (δ^{TMS}_{ppm}): 150.4 (s, C-6); 136.4 (s, C-7a'); 127.9 (s, C-3a'); 122.4 (d, C-2'); 121.8 (d, C-5'); 119.3 (d, C-6'); 119.1 (d, C-4'); 113.8 (s, C-3'); 111.0 (d, C-7'); 108.8 (t, C-13); 54.2 (d, C-4); 53.3 (s, C-2); 43.2 (d, C-5); 36.8 (d, C-1); 33.2, 31.9, 31.3 and 29.2 (4t, C-7 + C-8 + C-9 + C-10); 29.7 and 27.1 (2 qa, C-11 + C-12).

Fraction 10

Analytical t.l.c. (7% MeOH/EtOAc) showed the presence of two components. The mixture was separated on p.t.l.c. (7% MeOH/EtOAc) The higher R_f band proved to be makomakine.

The lower R_f band was extracted to give 100 mg of an alkaloid which proved to be identical with isopeduncularine, the major alkaloid isolated from *Aristotelia fruticosa* and discussed in Chapter 3.

Fraction 9

Analytical t.l.c. ($CHCl_3$:MeOH:EtOAc:NH_4OH, 1:5:13:0.03) showed the presence of three alkaloids. The mixture was separated by p.t.l.c. ($CHCl_3$:MeOH:EtOAc:NH_4OH, 1:5:13:.03). The highest R_f band proved to contain isopeduncularine.

A new alkaloid, named aristoserratenine, was isolated from the lowest R_f band (50 mg). It could not be crystallised, but had $[\alpha]_D^{19}$ + 58° (C, 0.9, $CHCl_3$); λ_{max} (MeOH): 259 nm (3.57), 226 nm (4.38); ν_{max} ($CHCl_3$): 3250 cm^{-1} (broad, HN); P.M.R. (δ ppm): 8.0 (1H, s, H-C_2); 7.15-7.6 (4H, multiplet, aromatic protons); 3.83 (1H, ddd, $J_{11/10exo}$ = 6.6 Hz, $J_{11/16}$ = 5.0 Hz, $J_{11/10endo}$ = 0.90 Hz, H-C_{11}); 3.16 (1H, td, $J_{18endo/18exo,19exo}$ = 14.0 Hz, $J_{18endo/19endo}$ = 5.5 Hz, H_{endo}-$C_{(18)}$; 2.37 (1H, dd, $J_{gem(10exo/10endo)}$ = 14.7 Hz, $J_{10exo/11}$ = 6.6 Hz, H_{exo}-C_{10}); 2.17 (1H, dqa, $J_{gem(15a/15b)}$ = 13.3 Hz, $J_{15a/14,16/19endo}$ = 2.5 Hz, H_a-C_{15}); 2.02 (1H, dt, $J_{16/11}$ = 5.0 Hz, $J_{16/15a,15b}$ = 2.5 Hz, H-C_{16}); 1.99 (1H, ddqa, $J_{gem(19endo/19exo)}$ = 14.0 Hz, $J_{19endo/18endo}$ = 5.5 Hz, $J_{19endo/18exo,14,15a}$ = 2.5 Hz, H_{endo}-C_{19}); 1.87 (1H, dd, $J_{gem(10endo/10exo)}$ = 14.7 Hz, $J_{10endo/11}$ = 0.9 Hz, H_{endo}-C_{10}); 1.66 (1H, dt, $J_{gem(15b/15a)}$ = 13.3 Hz, $J_{15b/14,16}$ = 2.5 Hz, H_b-C_{15}); 1.61 (1H, tdd, $J_{19exo/19endo,18endo}$ = 14.0 Hz, $J_{19exo/18exo}$ = 5.0 Hz, $J_{19exo/14}$ = 2.5 Hz, H_{exo}-C_{19}); 1.39 (1H, quintet, $J_{14/15a,15b,19a,19b}$ = 2.5 Hz, 1.00 (1H, ddd, $J_{gem(18exo/18endo)}$ = 14.0 Hz, $J_{18exo/19exo}$ = 5.0 Hz, $J_{18exo/19endo}$ = 2.5 Hz, H_{exo}-C_{18}); 1.0-1.16 (1H, broad, HN_b, exchangeable with D_2O); 1.22 and 1.17 (6H, 2s, 3H-C_{21} + 3H-C_{22}); 0.66 (3H, s, 3H-C_{20}); NOE experiment: Irrad.: 8.0 (H-C_2) → 3.16 (H_{endo}-C_{18}, relative integral change from 119.8 to 87.5); Irrad.: 3.16 → 8.0 (relative integral change from 78.5-74.5).[15] H.R.M.S.: m/e 294 (M^+, 70). Meas.: 294.2094;

calc. for $C_{20}H_{26}N_2$: 294.2096; 279 (100), 237 (48), 211 (53), 207 (28), 182 (57), 181 (35), 180 (51), 167 (37), 143 (36), 130 (38), 117 (14), 77 (57%). ^{13}C N.M.R. (δ^{TMS}_{ppm}): 178.7 (d, C-2); 155.7 (s, C-9); 139.3 (s, C-4); 127.6 (d, C-6); 125.5 (d, C-7); 124.8 (d, C-5); 120.6 (d, C-8); 70.8 (s, C-3); 54.0 (s, C-13); 53.4 (d, C-11); 46.8 (s, C-17); 46.2 (d, C-16); 39.5 (t, C-10); 36.0 and 27.4 (2 qa, C-21 + C-22); 32.2 (t, C-18); 30.2 (d, C-14); 25.2 and 23.7 (2t, C-15 + C-19); 19.7 (qa, C-20).

The middle R_f band was extracted to give 100 mg of a new alkaloid, named serratoline (XV), which crystallised from methanol as colourless rhombs, m.p. 157-160°C, $[\alpha]_D^{19}$ - 68.25° ($CHCl_3$); λ_{max} (MeOH): 263 nm (3.48), 227 nm (3.79); ν_{max} ($CHCl_3$); 3250-3350 cm^{-1} (-NH and -OH); P.M.R. (δ ppm): 7.15-7.55 (4H, multiplets, aromatic protons); 3.57 (1H, qa, $J_{11/10exo,10endo,16}$ = 2.9 Hz, H-C_{11}); 3.06 (1H, td, $J_{18endo/18exo,19exo}$ = 14.0 Hz, $J_{18endo/19endo}$ = 6.0 Hz, H_{endo}-C_{18}); 2.35 (1H, dd, $J_{10exo/10endo}$ = 14.25 Hz, $J_{10exo/11}$ = 2.9 Hz, H_{exo}-C_{10}); 1.98 (3H, multiplets, H-C_{16} + 2H-C_{15}); 1.77 (1H, tt, $J_{19exo/19endo,18endo}$ = 14.0 Hz, $J_{19exo/18exo,14}$ = 5.5 Hz, H_{exo}-C_{19}); 1.56 (3H, s, 3H-C_{20}); 1.52 (2H, multiplets, H_{endo}-C_{19} + H-C_{14}); 1.50 (1H, $J_{10endo/10exo}$ = 14.25 Hz, $J_{10endo/11}$ = 2.9 Hz, H_{endo}-C_{10}); 1.37 (1H, dd, $J_{18exo/18endo}$ = 14.0 Hz, $J_{18exo/19exo}$ = 5.5 Hz, H_{exo}-C_{18}); 1.35-1.25 (2H, exchangeable with D_2O, H-N_b + H-O); 1.30 and 1.25 (2 x 3H, 2s, 3H-C_{21} + 3H-C_{22}). H.R.M.S.: m/e 310 (M^+, 25). Meas.: 310.2039; calc. for $C_{20}H_{26}N_2O$: 310.2045, 296 (28), 295 (100), 277 (68), 227 (48), 183 (7), 182 (8), 181 (8), 180 (9), 173 (16), 159 (18), 146 (13), 130 (8), 91 (10), 77 (17). Analysis: Found: C, 73.53; H, 8.75; N, 8.18. Calculated for $C_{20}H_{26}N_2O$, CH_3OH: C, 73.63; H, 8.83; N, 8.18. ^{13}C N.M.R. (δ^{TMS}_{ppm}):

189.0 (s, C-2); 152.6 (s, C-9); 141.1 (s, C-4); 129.1 (d, C-6); 125.7 (d, C-7); 122.1 (d, C-5); 120.5 (d, C-8); 83.9 (s, C-3); 53.6 (s, C-13); 52.4 (d, C-11); 44.2 (d, C-16); 43.4 (t, C-10); 41.5 (s, C-17); 35.6 (d, C-14); 29.6 and 27.9 (2 qa, C-21 + C-22), 28.3, 26.4 and 24.4 (3t, C-18 + C-15 + C-19); and 23.6 (qa, C-20).

Fraction 8

Analytical t.l.c. (2.5% MeOH/EtOAc) showed the presence of three components. The mixture was subjected to p.t.l.c. (2.5% MeOH/EtOAc). The middle R_f band proved to contain isopeduncularine. The lowest R_f band was extracted and found to be serratoline. The amount of the component corresponding to the highest R_f band was too small for further studies.

Fraction 7

This fraction when subjected to p.t.l.c. (7% MeOH/EtOAc) separated into two bands. From the higher R_f band (after further purifications on p.t.l.c.) was isolated an oil (60 mg) which could not be induced to crystallise and gave a negative Ehrlich test. It was found to be a new alkaloid, aristomakine, $[\alpha]_D^{22}$ - 79.1° (C, 1.5, $CHCl_3$); λ_{max} (MeOH): 290 nm (3.71), 282.5 nm (3.77), 274 nm (sh, 3.75), 228 nm (4.53); ν_{max} ($CHCl_3$): 3400 cm^{-1} (HN, 3250 cm^{-1} (broad, HN); 1625 cm^{-1} (w, C=C); P.M.R. ($CDCl_3$, C_6D_6, δ ppm): 7.76 (1H, broad, exchangeable with D_2O, H-N_a); 7.0-7.4 (4H, multiplet, aromatic protons); 6.02 (1H, dt, $J_{13/14}$ = 10.0 Hz, $J_{allylic(13/15endo,15exo)}$ = 1.0 Hz, H-C_{13}); 5.72 (1H, dddd, $J_{14/13}$ = 10.0 Hz, $J_{14/15exo}$ = 5.0 Hz, $J_{14/15endo}$ = 3.0 Hz, $J_{allylic(14/12)}$ = 1.5 Hz, H-C_{14}); 3.44 (1H, ddd, $J_{11/10\ endo}$ = 11 Hz, $J_{11/10exo}$ = 5.0 Hz, $J_{11/12}$ = 3.5 Hz, H-C_{11}); 3.1

(1H, septet, $J_{20/21,22}$ = 6.5 Hz, H-C_{20}); 2.90 (1H, dd, $J_{gem(10exo/10endo}$ = 14.8 Hz, $J_{10exo/11}$ = 5.0 Hz, H_{exo}-C_{10}); 2.52 (1H, dd, $J_{12/11}$ = 3.5 Hz, $J_{allylic(12/14)}$ = 1.5 Hz, H-C_{12}); 2.30 (1H, dd, $J_{gem(10endo/10exo)}$ = 14.8 Hz, $J_{10endo/11}$ = 11.0 Hz, (H_{endo}-C_{10}); 2.04 (1H, ddtd, $J_{gem(15exo/15endo)}$ = 11.0 Hz, $J_{15exo/14}$ = 5.0 Hz, $J_{15exo/16exo,16endo}$ = 2.5 Hz, $J_{allylic(15exo/13)}$ = 1.0 Hz, H_{exo}-C_{15}); 1.93 (1H, broad, exchangeable with D_2O, H-N_b); 1.86 (1H, dt, $J_{gem(16endo/16exo}$ = 16.0 Hz, $J_{16endo/15endo,15exo}$ = 2.5 Hz, H_{endo}-C_{16}); 1.79 (1H, tddd, $J_{15endo/15exo,16exo}$ = 11.0 Hz, $J_{15endo/14}$ = 3.0 Hz, $J_{15endo/16endo}$ = 2.5 Hz, $J_{allylic(15endo/13)}$ = 1.0 Hz, H_{endo}-C_{15}); 1.63 (1H, ddd, $J_{gem(16exo/16endo)}$ = 16.0 Hz, $J_{16exo/15endo}$ = 11.0 Hz, $J_{16exo/15\ exo}$ = 2.5 Hz, H_{exo}-C_{16}); 1.36 (3H, s, 3H-C_{18}); 1.10 (6H, d, $J_{21,22/20}$ = 6.5 Hz, 3H-C_{21} + 3H-C_{22}). Mass spec.: m/e 294 (M^{+}, 80). Meas.: 294.2097; Calc. for $C_{20}H_{26}N_2$: 294.2096; 279 (10), 251 (6), 240 (10), 236 (10), 225 (22), 183 (34), 182 (34), 181 (33), 180 (20), 170 (27), 130 (25), 124 (100, $C_8H_{14}N$), 98 (58), 85 (90). ^{13}C N.M.R. (δ^{TMS}_{ppm}): 137.6 (s, C-9); 136.3 (s, C-2); 129.8 (d, C-13); 127.2 (s, C-4); 123.1 (d, C-14); 121.3 (d, C-6); 119.3 (d, C-7); 118.1 (d, C-5); 110.6 (d, C-8); 108.3 (s, C-3); 51.5 (d, C-11); 46.4 (d, C-20); 44.7 (d, C-12); 35.4 (s, C-17); 34.7 (t, C-15); 29.9 (qa, C-18); 24.7 and 22.7 (2t, C-16 + C-10); 22.3 and 21.8 (2 qa, C-21 + C-22).

The lower band was extracted and 60 mg of an alkaloid was isolated which was proved to be serratoline.

Fraction 6

Analytical t.l.c. (silica gel - 0.5 N KOH, 2.5% MeOH/$CHCl_3$) showed the presence of three components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 2.5% MeOH/$CHCl_3$). The

middle and the highest R_f bands proved to contain aristoteline and serratoline respectively.

The lowest R_f band was extracted to give 60 mg of a new alkaloid, isosorelline (XX), which gave a positive Ehrlich test and crystallised from methanol as colourless crystals, m.p. 160-162°C, $[\alpha]_D^{21.5}$ + 120° (C, 0.62, $CHCl_3$); λ_{max} (MeOH): 290 nm (3.62), 282.5 nm (3.67), 273 nm (sh, 3.63), 224 nm (4.46); ν_{max} ($CHCl_3$): 3480 cm^{-1} (-NH), 3250-3180 cm^{-1} (br), 1630 cm^{-1} (m); P.M.R. (δ ppm): 8.2 (1H, br.s, exchangeable with D_2O, H-N_a); 7.7-7.05 (4H, multiplets, aromatic protons); 6.99 (1H, s, H-$C_{2'}$); 6.33 (1H, d, $J_{7/8}$ = 9.6 Hz, H-C_7); 5.93 (1H, dd, $J_{8/7}$ = 9.6 Hz, $J_{8/1}$ = 6.0 Hz , H-C_8); 5.08 (1H, d, $J_{13a/5}$ = 2.1 Hz, H_a-C_{13}); 4.74 (1H, d, $J_{13b/5}$ = 2.1 Hz, H_b-C_{13}); 3.48 (1H, td, $J_{4/12a,12b}$ = 6.4 Hz, $J_{4/5}$ = 2.7 Hz, H-C_4); 2.9-2.6 (2H, multiplets, H_a, H_b-C_{12}); 2.39 (1H, m, H-C_5); 2.1-2.0 (2H, multiplets, H_a-C_9 + H-C_1); 1.76 (1H, dm, $J_{9b/9a}$ = 12.8 Hz, H_b-C_9); 1.28 and 1.02 (2 x 3H, 2s, 3H-C_{10} + 3H-C_{11}). H.R.M.S.: m/e 292 (M^+, 24). Meas.: 292.1921; calc. for $C_{20}H_{24}N_2$: 292.1939), 277 (17), 199 (16), 162 (100), 159 (37), 130 (44), 117 (11), 105 (13), 92 (9), 91 (23). Analysis: Found: C, ; H, ; N, . Calculated for $C_{20}H_{24}N_2$: C, ; H, ; N, %.

Fraction 5

Analytical t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$) showed the presence of at least three components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$). The highest R_f band proved to contain serratoline.

The lowest R_f band yielded on extraction a new alkaloid, isohobartine (35 mg) (XVIII) which gave a positive Ehrlich test. It

crystallised from chloroform, on chilling, as colourless crystals, m.p. 134-135°C, $[\alpha]_D^{19}$ - 30° (C, 0.27, $CHCl_3$); λ_{max} (MeOH): 291 nm (3.83), 282 nm (3.85), 274 nm (sh, 3.84), 223 nm (4.62); ν_{max} ($CHCl_3$): 3400 cm^{-1} (-NH); 3200-3300 cm^{-1} (-NH); P.M.R. (δ ppm): 8.27 (1H, br.s, exchangeable with D_2O, H-N_a); 7.65-7.0 (4H, multiplets, aromatic protons); 7.03 (1H, s, H-$C_{2'}$); 5.65 (1H, septet, $J_{7/8exo,8endo,5,11}$ = 1.8 Hz, H-C_7); 3.55 (1H, td, $J_{4/10a,10b}$ = 7.0 Hz, $J_{4/5}$ = 2.7 Hz, H-C_4); 2.85 (2H, d, $J_{10a,b/4}$ = 7.0 Hz, $H_{a,b}$-C_{10}); 2.32 (1H, dm, $J_{8endo/8exo}$ = 19.0 Hz, H_{endo}-C_8); 2.20 (1H, m, H-C_5); 2.10 (1H, dm, $J_{9a/9b}$ = 13.0 Hz, H_a-C_9); 2.05 (1H, dm, $J_{8exo/8endo}$ = 19.0 Hz, H_{exo}-C_8); 1.81 (3H, d, $J_{11/7}$ = 1.8 Hz, 3H-C_{11}); 1.62 (1H, dt, $J_{9b/9a}$ = 13.0 Hz, $J_{9b/5,1}$ = 3.3 Hz, H_b-C_9); 1.50-1.60 (1H, broad, exchangeable with D_2O, H-N_b); 1.49 (1H, m, H-C_1); 1.25 + 1.20 (2 x 3H, 2s, 3H-C_{12} + 3H-C_{13}). H.R.M.S.: m/e 294 (M^+, 17). Meas.: 294.2091; calc. for $C_{20}H_{26}N_2$: 294.2096, 279 (48), 199 (3), 164 (100), 159 (8), 130 (24), 93 (12), 91 (8).

From the middle R_f band was isolated another alkaloid which proved to be aristoteline.

Fraction 4

Crystallisation from methanol afforded 500 mg of colourless crystals of aristoteline. The mother liquor showed aristoteline as the major component together with at least two minor bases which could not be further purified.

Fraction 3

Analytical t.l.c. (silica gel - 0.5 N KOH, 7% MeOH/$CHCl_3$) showed the presence of aristoteline with traces of two other bases in insufficient amount for further studies.

Fraction 2

Analytical t.l.c. (silica gel - 0.5 N KOH, 7% MeOH/$CHCl_3$) showed the présence of one major and three minor components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$, multiple development) into four bands. The first (highest) R_f band proved to contain aristoteline.

The third (from the top) R_f band was extracted to give 20 mg of a base which proved to be isohobartine.

From the fourth (lowest) R_f band was isolated a new alkaloid, XXI, which gave a negative Ehrlich test, and crystallised from methanol as colourless crystals, m.p. 249-250°C, $[\alpha]_D^{19}$ - 150° (C, 1.0, MeOH); λ_{max} (MeOH): 285 nm (3.18), 254 nm (3.76); 217 nm (4.35); ν_{max} (Nujol): 3400-3150 cm^{-1} (br, -NH); 1700 cm^{-1} (s, >C=O); P.M.R. (δ ppm): 9.2 (1H, br. s, exchangeable with D_2O, H-N_a); 7.5-6.8 (4H, multiplets, aromatic protons); 3.80 (1H, dd, $J_{11/10a}$ = 6.0 Hz, $J_{11/16}$ = 5.5 Hz, H-C_{11}); 3.03 (1H, td, $J_{18endo/18exo,19exo}$ = 13.5 Hz, $J_{18endo/19endo}$ = 5.5 Hz, H_{endo}-C_{18}); 2.7-2.45 (2H, multiplets); 2.25-2.05 (1H, dm, J = 13.5 Hz); 1.9-1.3 (5H, multiplets); 1.30-1.25 (2H, one proton is exchangeable with D_2O, H-N_b); 1.24 and 1.2 (2 x 3H, 2s, 3H-C_{21} + 3H-C_{22}); 0.92 (3H, s, 3H-C_{20}); 0.6-0.9 (1H, m). H.R.M.S.: m/e 310 ($M^{+\cdot}$, 22). Meas.: 310.2037; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (100); 267 (6), 178 (7); 174 (24), 165 (4), 164 (4), 150 (4), 155 (4), 137 (5), 84 (12), 83 (16), 81 (12), 146 (4).

Extraction of the second R_f band afforded 30 mg of a new alkaloid, aristomakinine (XIX), as an oil which could not be crystallised. It had $[\alpha]_D^{19}$ - 72° (C, 0.5, MeOH); λ_{max} (MeOH): 290 nm (3.49), 282.5 nm (3.55), 275 nm (sh, 3.53), 229 nm (3.97); ν_{max} ($CHCl_3$): 3480 cm^{-1} (-NH); P.M.R. (δ ppm): 7.96 (1H, br. s, exchangeable with

D_2O, H-N_a); 7.5-7.0 (4H, multiplets, aromatic protons); 5.76 (2H, s, H-C_{13} + H-C_{14}); 3.6 (1H, m, H-C_{11}); 3.0-2.65 (1H, m), 2.5-2.2 (2H, multiplets); 2.1-1.6 (4H, two protons exchangeable with D_2O, multiplets); 1.5-1.2 (2H, multiplets); 1.37 (3H, s, 3H-C_{18}). H.R.M.S.: m/e 252 (M^+, 100). Meas.: 252.1646; calc. for $C_{17}H_{20}N_2$: 252.1626, 237 (7), 235 (9), 220 (23), 183 (68), 182 (30), 181 (28), 180 (16), 170 (72), 158 (21), 130 (30), 82 (23), 77 (24).

$LiAlH_4$ - Reduction of aristotelinone (IV)

Aristotelinone (33 mg, 0.1 mmol) was partly dissolved in 10 ml of dry THF and added to THF (5 ml) containing lithium-aluminium hydride (10 mg) in a flask fitted with a magnetic stirrer and a reflux condenser. The mixture was refluxed for 5½ hr. The excess LAH was reacted with the calculated amount of water. Sodium sulphate (anhydrous) was added to coagulate the lithium aluminate formed which was finally filtered. The basic material was then extracted from the filtrate with chloroform, which was dried (Na_2SO_4) and evaporated to dryness to give 30 mg of a mixture.

Analytical t.l.c. (20% MeOH/$CHCl_3$) revealed the presence of two components. The mixture was separated by p.t.l.c. (20% MeOH/$CHCl_3$). From the higher R_f band was extracted 13 mg of a dihydro-product (VI) which crystallised from MeOH-ether in colourless crystals, m.p. 167-168°C; λ_{max} (MeOH): 290 nm (3.39), 282 nm (3.46), 274 nm (sh, 3.45), 226 nm (3.98); ν_{max} ($CHCl_3$): 3250 cm^{-1} (broad, HN, -OH); P.M.R. (δ ppm): 7.88 (1H, broad, exchangeable with D_2O, indolic N*H*); 7.1-7.6 (4H, multiplet, aromatic protons); 3.6-3.7 (2H, multiplet); 3.05 (1H, td, J = 13.5, 7.5 Hz); 2.45 (1H, dd, J = 14.5, 2.5 Hz), 1.6-2.0 (8 protons, multiplet); 1.58 (3H, s); 1.32 (3H, s); 1.26

(3H, s). H.R.M.S.: m/e 310 (M^+, 21). Meas.: 310.2045; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (82), 277 (23), 253 (8), 227 (28), 180 (15), 159 (20), 146 (11), 130 (12), 84 (100%).

The lower R_f band was extracted to give 12 mg of a mixture which again showed the presence of two components when an analytical plate (silica-gel impregnated with 0.5 M KOH, 2.5% MeOH/$CHCl_3$) was run. The mixture was separated on p.t.l.c. using the abovementioned solvent system. The component (6 mg) with the higher R_f value was crystallised from MeOH as colourless crystals of aristoteline, II, m.p. 83-85°C (solvate), 163.5-164°C (after drying); λ_{max} (MeOH): 291 nm (3.67), 282 nm (3.72); 228 nm (4.32); ν_{max} ($CHCl_3$): 3400 cm^{-1} (HN), 3300 cm^{-1} (HN); Mass spec.: 294 (M^+, 90%), 279 (100), 237 (58), 222 (27), 211 (75), 182 (43), 180 (36), 167 (31), 143 (37), 130 (22), 84 (29%). The identity of this compound was established by direct comparison of its m.p., mixed m.p., [α], R_f, u.v., i.r., and m.s. with authentic aristoteline isolated earlier.[11]

The other component (3 mg) corresponding to the lower R_f band was obtained as an oil which was shown to be the C-10 epimer of dihydroaristotelinone and was named epi-dihydroaristotelinone (V). It had λ_{max} (MeOH): 290 nm (3.73), 282.5 nm (3.76), 226 nm (4.51), ν_{max} ($CHCl_3$): 3400-3300 cm^{-1} (HN), H.R.M.S.: m/e 310 (M^+, 26). Meas.: 310.2045; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (8), 292 (73), 277 (91), 237 (40), 235 (100), 220 (46), 183 (15), 182 (18), 181 (62), 180 (40), 167 (14), 149 (19), 71 (34).

$NaBH_4$-Reduction of aristotelinone

Aristotelinone (29 mg, 0.09 mmole) was dissolved in 10 ml of ethanol containing 10 drops of water, excess sodium borohydride (20 mg)

was added, and the solution was stirred for 20 hr. The excess $NaBH_4$ was reacted with added methanol. The solvent was evaporated off *in vacuo*, and the residue was treated with water (20 ml) and extracted with chloroform (3 x 20 ml). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 27 mg of a single compound (93% yield) which crystallised from MeOH as colourless crystals, m.p. 203-204°C; λ_{max} (MeOH): 290 nm (3.73), 282.5 nm (3.76), 226 nm (4.50); ν_{max} ($CHCl_3$): 3400-3300 cm^{-1} (HN, OH); P.M.R. (ppm): 8.90 (1H, broad, exchangeable with D_2O, H-N_a); 7.9-7.0 (4H, multiplet, aromatic protons); 5.22 (1H, d, $J_{10/11}$ = 5.0 Hz, H_{eq}-C_{10}); 3.55 (1H, dd, $J_{11/10}$ = 5.0 Hz, $J_{11/16}$ = <3 Hz, H-C_{11}); 2.5-1.5 (8H, multiplet); 1.45, 1.28 and 1.10 (3 x 3H, 3s, 3H-C_{20} + 3H-C_{21} + 3H-C_{22}). H.R.M.S.: m/e 310 ($M^{+\cdot}$, 27). Meas.: 310.2045; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (10), 292 (72), 277 (90), 237 (49), 235 (100), 220 (45), 193 (60), 183 (17), 182 (18), 181 (67), 180 (38), 167 (17), 149 (20), 71 (34).

This dihydroaristotelinone proved to be the same as epi-dihydroaristotelinone (V). Their identity has been established by comparison of their R_f, u.v., i.r., p.m.r. and mass spectra.

Reduction of makonine (VII)

To a solution of makonine (25 mg) in aqueous ethanol (10 ml, 95%) was added 30 mg of sodium borohydride, and the solution was stirred for 18 hr. The excess $NaBH_4$ was reacted with methanol. The solvent was evaporated to dryness *in vacuo*, the residue was treated with chloroform-water (30 ml, 1:1) and extracted with chloroform (4 x 20 ml). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give

25 mg (99% yield) of a single compound, tetrahydromakonine which crystallised from methanol without further purification as colourless crystals, m.p. 203-204°C. It had identical t.l.c. and spectroscopic data (u.v., i.r., p.m.r. and m.s.) to epi-dihydroaristotelinone (V). A mixed m.p. showed no depression.

LAH-Reduction of tetrahydromakonine (V)

A solution of 10 mg (.03 mmole) of tetrahydromakonine ($\tilde{\sim}$ epi-dihydroaristotelinone) in 10 ml of dry tetrahydrofuran was added to 10 mg of lithium aluminium hydride in 5 ml of THF and refluxed for 6 hr. The excess LAH was reacted with water, and extracted with chloroform (3 x 15 ml). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 8 mg of a residue. It was purified by p.t.l.c. (silica-gel impregnated with 0.5 M KOH, 10% MeOH/$CHCl_3$) to give 4 mg (42% yield) of a compound which crystallised from methanol as square prisms of aristoteline, m.p. 83-85° (solvate), 163-164°C (after drying). The identity of this compound was likewise established by direct comparison of its m.p., mixed m.p., [α], R_f, u.v., i.r., and mass spectra with authentic aristoteline.

Oxidation of aristotelinone

A mixture of 49 mg (0.16 mmol) of aristotelinone and 303.5 mg (0.64 mmol) of mercuric acetate in 20 ml of tetrahydrofuran was refluxed for 20 hr, cooled to room temperature and treated with 2 ml of 1M aqueous thioacetamide solution. The mixture was again boiled for 2 hr to remove completely the hydrogen sulphide formed, filtered through hyflo-supercell, basified with ammonia (d, 0.88) and extracted with chloroform. The combined chloroform extracts were

dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 40 mg of a residue. Purification by p.t.l.c. (ethyl acetate) afforded 12 mg (25% yield) of a base which crystallised from methanol as hexagonal crystals, m.p. 310-312°C (d). The oxidation product had identical t.l.c., R_f, [α], u.v., i.r., p.m.r. and m.s. to natural makonine. A mixed m.p. showed no depression.

Acid-catalysed cyclisation of makomakine (IX)

To 30 mg of makomakine was added 1 ml of 47% hydrobromic acid, and the mixture was stirred at room temperature (18°C) for 18 hr, then basified with ammonia (d, 0.88) and extracted with chloroform. The $CHCl_3$-extract was dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 28 mg of a residue which was separated by p.t.l.c. (silica-gel impregnated with 0.5 M KOH, 2.5% MeOH/$CHCl_3$: double development). The major component (10 mg, 33% yield) with the highest R_f value was extracted which gave a negative Ehrlich test. It crystallised from methanol as square prisms of aristoteline, m.p. 83-85°C (solvate), 163-164°C (after drying). The identity was established by direct comparison of its R_f, [α], i.r., u.v., p.m.r., mass spectra and also melting point and mixed melting points with authentic aristoteline.

Acid-catalysed cyclisation of aristoserratenine (X)

Aristoserratenine (15 mg) was dissolved in 2 ml of 5% (w/v) sulphuric acid, and the resulting solution was refluxed for 8 hr, then cooled to room temperature, basified with ammonia (d, 0.88) and extracted with chloroform (3 x 15 ml). The combined chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 13 mg of a residue. Purification by p.t.l.c.

(silica-gel impregnated with 0.5 M KOH, 2.5% MeOH/$CHCl_3$) afforded 7 mg of a base (47% yield) as the only major component. It crystallised from methanol as colourless crystals, m.p. 82-85°C (solvate), 162-163.5°C (after drying, lit.[11] value 163-164°C), and proved identical to natural aristoteline by a comparison of their [α], $R_{f's}$, u.v., i.r., and mass spectra, m.p. and mixed m.p.

Reduction of aristoserratine

To a solution of 17 mg (.06 mmole) of aristoserratine in 5 ml of 95% ethanol was added 20 mg of sodium borohydride. The solution was stirred for 18 hr, then the excess $NaBH_4$ was reacted with methanol and the solvent was evaporated completely *in vacuo*. The residue was diluted with 20 ml of chloroform-water (1:1) and extracted with chloroform (3 x 20 ml). The combined chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Analytical t.l.c. (50% MeOH/$CHCl_3$) on the residue (15 mg) showed the presence of two components. The mixture was separated to give 9.5 mg (56% yield) of a dihydro compound which crystallised from methanol as colourless crystals, m.p. 219-223°C (d), λ_{max}: 290 nm (3.12), 282 nm (3.19), 274 nm (sh, 3.17), 228 nm (3.80); ν_{max} (Nujol): 3400 cm^{-1} (HN), 3300-3200 cm^{-1} (HN, -OH); H.R.M.S.: m/e 310 (M^+, 100). Meas.: 310.2041; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (60), 277 (14), 253 (40), 236 (15), 228 (10), 227 (80), 220 (11), 209 (12), 184 (24), 183 (28), 182 (40), 181 (20), 180 (12), 167 (16), 143 (26), 122 (27).

Reduction of serratoline (XV)

Serratoline (21 mg, 0.07 mmole) was dissolved in 10 ml of ethanol containihg 10 drops of water. Excess sodium borohydride was added and the solution was stirred at room temperature for 20 hr. The excess sodium borohydride was reacted with methanol and the solvents were evaporated off *in vacuo*. The residue was treated with 20 ml of water and extracted with chloroform (20 ml x 4). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 19.5 mg of an oil (92% yield), which proved to be dihydroserratoline (XVII) with λ_{max} (MeOH): 291 nm (3.29), 239 nm (3.66), 228 nm (sh, 3.63); ν_{max} ($CHCl_3$); 3300-3150 cm^{-1} (-NH + -OH); P.M.R. (δ ppm): 7.3-6.6 (4H, multiplets, aromatic protons); 3.8 (1H, br. s, exchangeable with D_2O, -O*H*); 3.5-3.3 (2H, multiplets); 2.6 (1H, m); 1.9-1.1 (8H, multiplets), 1.4 (1H, m), 1.3-1.2 (1H, br., exchangeable with D_2O, H-N_b); 1.22 (6H, s, 3H-C_{21} + 3H-C_{22}); 1.18 (3H, s, 3H-C_{20}). Mass Spec.: m/e 312 (M^{+}, <1%); 294 (81, M-18); 279 (100), 237 (77), 222 (28), 211 (78), 194 (23), 183 (22), 182 (43), 181 (36), 180 (39), 167 (38), 143 (41), 130 (17).

Dehydration of dihydroserratoline (XVII)

Dihydroserratoline (XVII) (15 mg) was placed in a flask fitted with a reflux condenser. Aqueous oxalic acid (10 ml, 6%) was added and the mixture was refluxed for 6 hr.. The reaction mixture was cooled, basified with potassium carbonate, and extracted with chloroform (15 ml x 4). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 12 mg of a single compound which crystallised from methanol as colourless crystals, m.p. 83-85°C (solvated), 163-164°C (after drying).

It proved to be identical with naturally-occurring aristoteline by comparison of their [α], $R_{f's}$, i.r., p.m.r., u.v. and mass spectra. The two samples had also identical m.p. and m.m.p.

Attempted base-catalysed rearrangement of serratoline (XV)

Serratoline (10 mg) was dissolved in 10 ml of methanol, and 1 ml of 2N sodium hydroxide solution was added. The resulting mixture was refluxed for 5 hr, and then evaporated to dryness *in vacuo*. The residue was treated with water (20 ml) and extracted with chloroform (20 ml x 4). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated *in vacuo* to give 8 mg of unreacted serratoline.

Acid-catalysed rearrangement of serratoline (XV)

Serratoline (45 mg, 0.15 mmol) was dissolved in 20 ml of 5% (w/v) sulphuric acid in a 50 ml flask. The solution was refluxed for 15 hr, then cooled, basified with ammonia (d, 0.88) and extracted with chloroform (20 ml x 4). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to yield 40 mg of a residue. A t.l.c. comparison with serratoline indicated complete reaction.

Analytical t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$) showed the presence of one major and two minor components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$). The highest R_f band was extracted to give 30 mg (67% yield) of the major product, which proved identical with aristotelone (XVI). It crystallised from methanol as colourless crystals, m.p. 217-218°C (lit.[10] m.p. 218-222°C), $[\alpha]_D^{19}$ + 63° (C, 0.40, MeOH); λ_{max} (MeOH): 284 nm (3.49), 254 nm (4.31), 217 nm (4.51); ν_{max} ($CHCl_3$):

3200-3350 cm^{-1} (-NH), 1665 cm^{-1} (s), 1620 cm^{-1}; P.M.R. (δ ppm): 8.2 (1H, br. s, exchangeable with D_2O, H-N_a); 7.3-6.8 (4H, multiplets, aromatic protons); 3.8 (1H, m); 2.97 (1H, m); 2.5-2.25 (1H, m), 2.2-1.5 (6H, multiplets); 1.4-1.2 (2H, one proton is exchangeable with D_2O), 1.18 and 1.15 (2 x 3H, 2s, 3H-C_{21} + 3H-C_{22})); 0.57 (3H, s, 3H-C_{20}); H.R.M.S.: m/e 310 (M^+, 50). Meas.: 310.2045; calc. for $C_{20}H_{26}N_2O$: 310.2045; 295 (22), 174 (55), 173 (24), 164 (100), 149 (30), 146 (16), 111 (16), 97 (28), 84 (44), 83 (30), 77 (12).

The minor products were obtained in amounts too small for adequate characterisation.

Synthesis of serratoline (XV) from aristoteline (II)

Aristoteline (80 mg) was dissolved in hot petroleum ether (200 ml). A trace of benzoyl peroxide (about 2-3 mg) was added, and the solution was kept for 3 days. The solvent was then removed *in vacuo* and the residue was agitated with a mixture of 2 N aqueous sodium hydroxide (10 ml), sodium dithionite (400 mg) and ether (15 ml) for 1 hr. The ether layer was separated and the aqueous layer was extracted with more ether (20 ml x 3). The combined ether extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 70 mg of a residue. Analytical t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$) indicated the presence of one major (medium R_f) and one minor (highest R_f) product together with some unreacted aristoteline (lowest R_f). The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$) and the middle R_f band was extracted to give 11 mg of serratoline (XV), which crystallised from MeOH as colourless crystals, m.p. 157-160°C. Its identity was established by a comparison of its R_f, [α], i.r., u.v., m.s., m.p. and m.m.p. with those of an authentic specimen.

Acid-catalysed cyclisation of isohobartine (XVIII)

To 20 mg of isohobartine was added 1 ml of 47% hydrobromic acid, then the resulting mixture was stirred at room temperature (19°C) for 18 hr. The solution was diluted with water (20 ml), basified with ammonia (d, 0.88) and extracted with chloroform (20 ml x 4). The combined chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 13 mg of a residue. Analytical t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$) showed the presence of two components, one of which corresponded to the unreacted isohobartine. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 5% MeOH/$CHCl_3$, multiple development) and the major band (higher R_f value) was extracted to give 6 mg (30% yield) of a product which crystallised from methanol as colourless crystals, m.p. 82-85° (solvated), 162.5-164.5° (after drying). The product proved to be identical with naturally-occurring aristoteline by a direct comparison of their R_f's, [α], u.v., i.r., m.s., m.p. and m.m.p.

Reduction of tasmanine (XXI)

To a solution of tasmanine (20 mg, 0.06 mmole) in 10 ml of dry tetrahydrofuran (THF) was added 15 mg of lithium aluminium hydride (LAH) in 5 ml of THF and the mixture was refluxed for 5 hr. The excess LAH was reacted with added water. The solvents were removed on a rotary evaporator, the residue was treated with water (20 ml) containing a few drops of 5% sodium hydroxide solution, and the mixture was extracted with chloroform (20 ml x 4). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to yield 14 mg of a residue. Analytical t.l.c. (10% MeOH/$CHCl_3$) showed the presence of one major

(lower R_f) and one minor component. The mixture was separated by p.t.l.c. (10% MeOH/$CHCl_3$) and the lower band was extracted to give 6 mg of the major product, which crystallised from methanol as colourless crystals of aristoteline. The identity of this reduction product was established by a direct comparison of its R_f, [α], i.r., u.v., m.s., m.p. and m.m.p. with those of naturally-occurring aristoteline.

Introduction of an isopropyl group into aristomakinine (XIX)

To a cold (≈0°C) stirred solution of aristomakinine (17 mg, 0.07 mmol), acetone (2 ml) and sodium acetate (25 mg) in 2 ml of glacial acetic acid containing 3 ml of water, excess sodium borohydride (≈50 mg) was added over 10 min. The mixture was made basic with dil. ammonia and extracted with chloroform (10 ml x 3). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 17 mg of an oil.

Analytical t.l.c. (silica gel - 0.5 N KOH, 2.5% EtOH/$CHCl_3$) showed the presence of a small amount of the unreacted material together with a major compound (higher R_f). The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 2.5% EtOH/$CHCl_3$). The higher R_f band was extracted to yield 8.5 mg (≈50% yield) of a product which proved to be aristomakine (XIII).[13] Its identity was established by a comparison of its R_f, [α], i.r., p.m.r., u.v., and mass spectra with those of naturally-occurring aristomakine.

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CHAPTER 3

Alkaloids of *Aristotelia fruticosa* (Hook. f.)

I. Results and Discussion

Aristotelia fruticosa is a small tree of up to two metres in height growing throughout New Zealand except north of Auckland. The plant material, roots, stems and leaves (1.75 Kg) were collected from around Rotorua. Extraction by standard methods yielded about 0.02% of crude alkaloids. The mixture was separated into five components by preparative thin-layer chromatography (p.t.l.c.). The major alkaloid, which was also found in *Aristotelia serrata*, proved to be a stereoisomer of peduncularine.[3] The structures of two of the minor alkaloids are also discussed. The structures of the remaining pair of minor alkaloids have been presented in the previous chapter.

1. The structure of fruticosonine

The minor base, fruticosonine, crystallised from anhydrous ether as square prisms, m.p. 120-121°C, $[\alpha]_D^{20}$ + 45.7° ($CHCl_3$), with a molecular formula $C_{20}H_{28}N_2O$ as found by elemental analysis. The ultraviolet absorption spectrum (Figure 2) shows that it has an indole nucleus present. In the P.M.R. spectrum of fruticosonine there is a one-proton doublet (J = 1.7 Hz) at 7.02 ppm which indicates that either the 2- or the 3-position of the indole nucleus is unsubstituted, and this conclusion is supported by a positive Ehrlich test. Moreover, the mass spectrum of fruticosonine shows a strong ion peak at m/e 130 together with the complementary ion peak at m/e 182, which shows that it is the indole-3 position that is substituted.

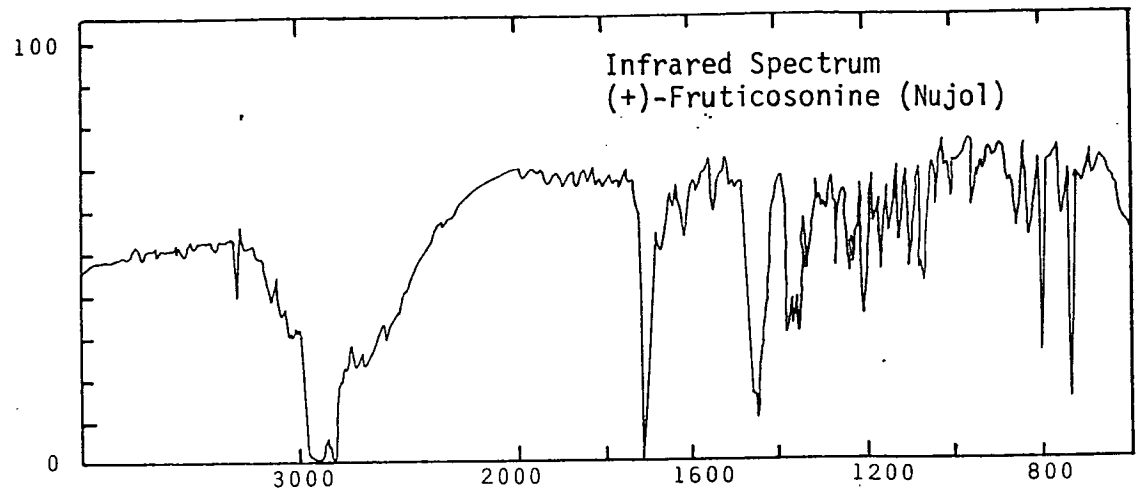


Figure 1.

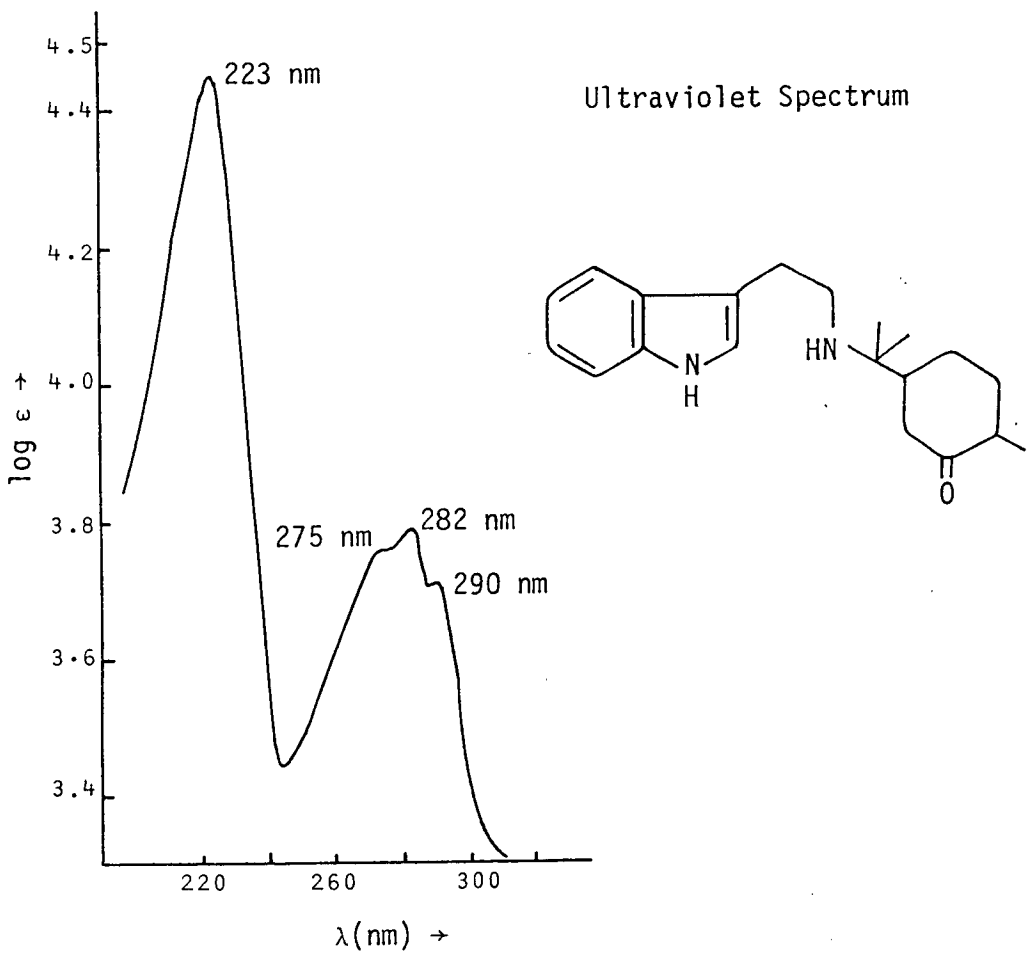


Figure 2.

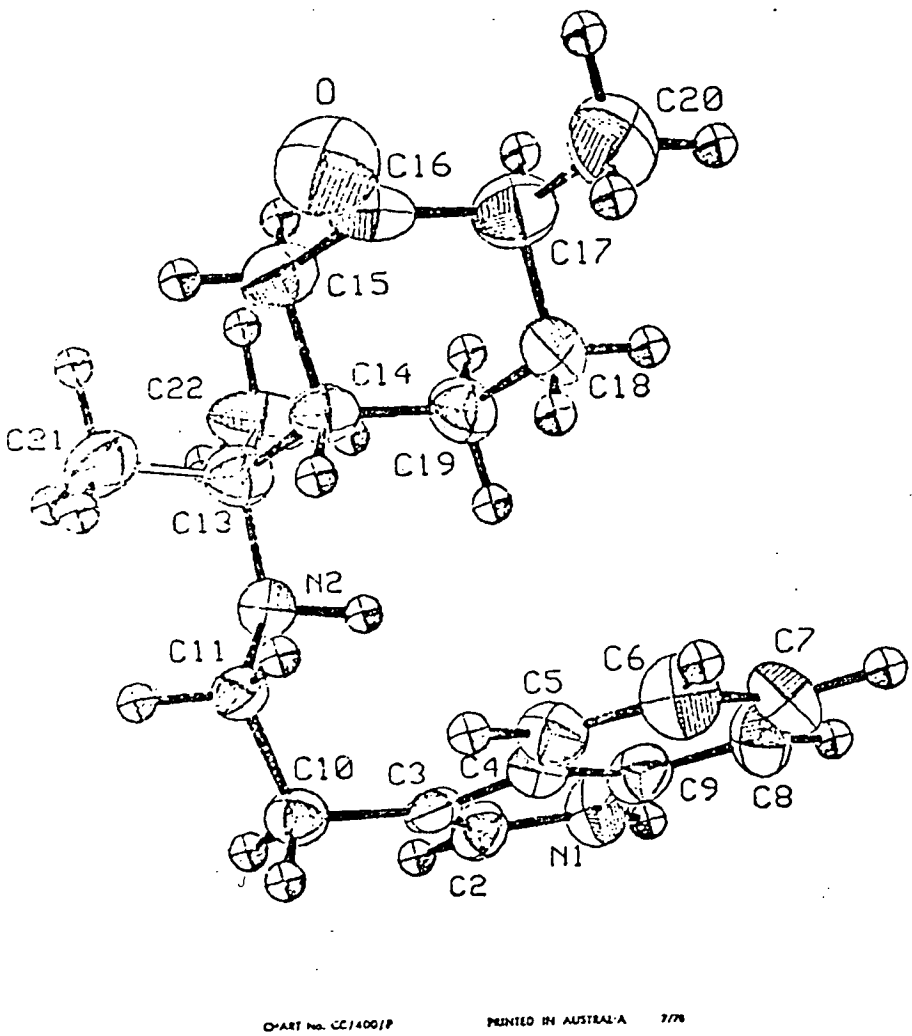
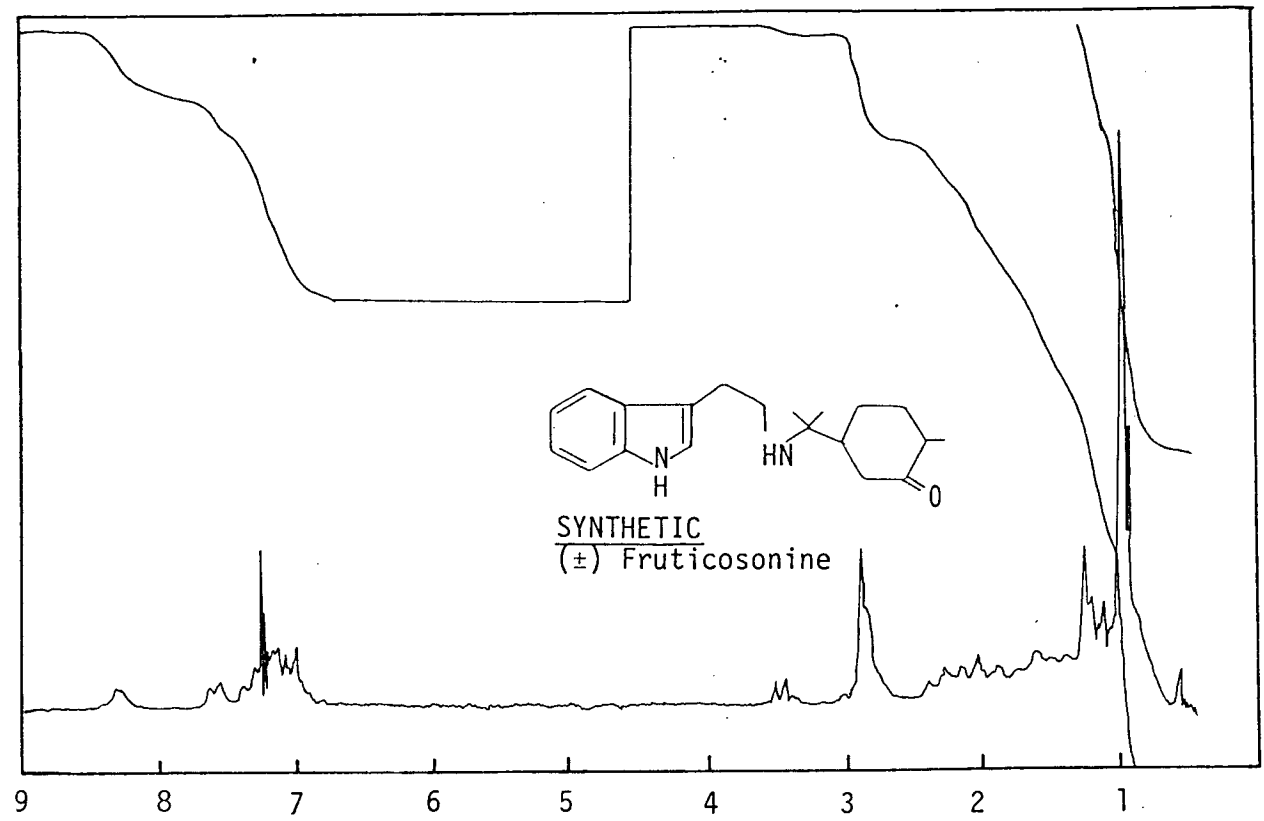
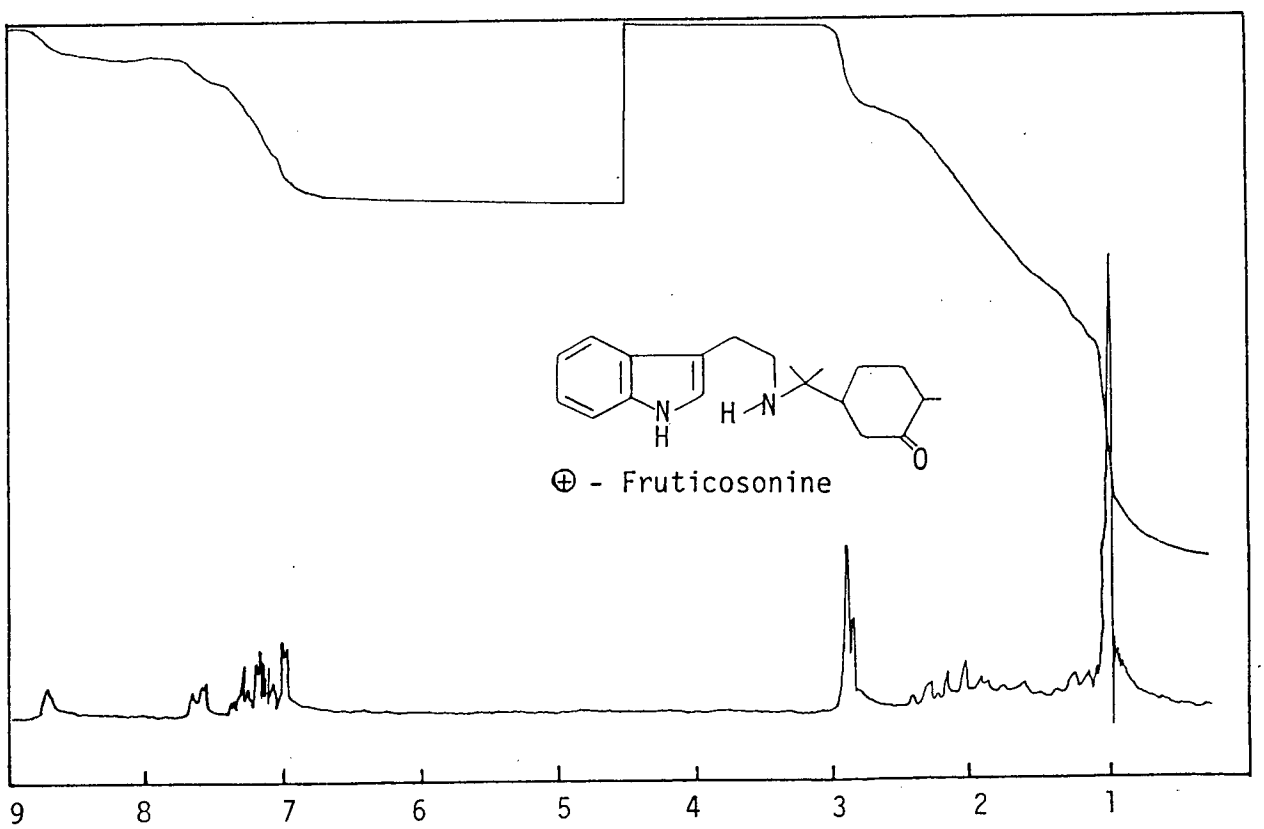


Figure 3. X-ray crystal structure of fruticosonine


SYNTHETIC
(±) Fruticosonine
9
8
7
6
5
4
3
2
1


⊕ - Fruticosonine
9
8
7
6
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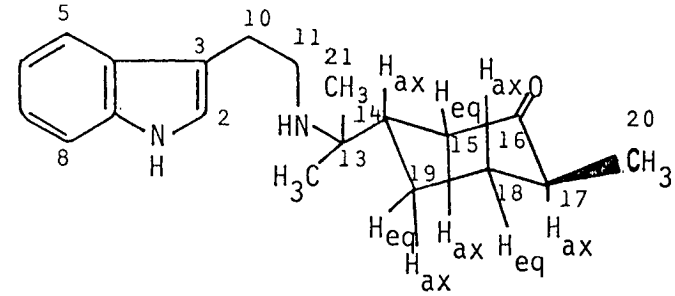
4
3
2
1

Figure 4.

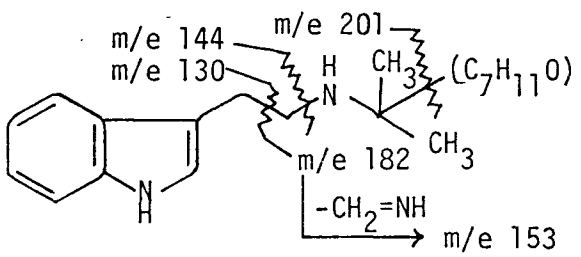
Table I. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of protons in the pmr spectrum of Fruticosonine (II).



Protons	H-C(14)	H_{ax}-C(15)	H_{eq}-C(15)	H-C(17)	H_{ax}-C(18)	H_{eq}-C(18)	H_{ax}-C(19)	H_{eq}-C(19)	3H-C(20)	Multiplicities	Chemical shifts
H-C(14)		13.0	3.5				13.0	3.5		txt	1.76
H_{ax}-C(15)	13.0		13.0							t	2.03
H_{eq}-C(15)	3.5	13.0								dxd	2.34
H-C(17)					13.0				6.5	dxqa	2.19
H_{ax}-C(18)				13.0		13.0	13.0	3.5		qaxd	1.16
H_{eq}-C(18)					13.0		3.5	3.5		dxt	1.95
H_{ax}-C(19)	13.0				13.0	3.5		13.0		qaxd	1.33
H_{eq}-C(19)	3.5				3.5	3.5	13.0			dxqa	1.63
3H-C(20)				6.5						d	.98

The oxygen atom is present as a carbonyl group, as shown by a strong band at 1710 cm^{-1} in the infrared absorption spectrum (Figure 1) of fruticosonine. Since there is no olefinic proton in the P.M.R. spectrum, there must be only one more ring system in addition to the indole nucleus. The P.M.R. spectrum shows two exchangeable protons, one 6-proton singlet at 0.99 ppm for the two geminal C-methyl groups, and also a 3-proton doublet (J = 6.5 Hz) at 0.98 ppm ($3H\text{-}C_{20}$).

From the strong ion peaks at m/e 130, 144, 182 (base peak) and 201 in the mass spectrum (Scheme 1), a partial structure of type (I) can be put forward for fruticosonine.



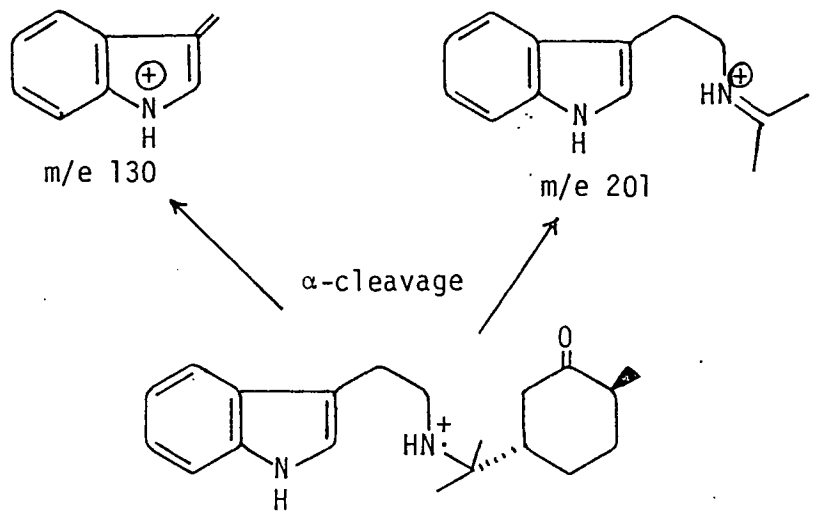
I

The two methylene groups between the indole ring and the aliphatic nitrogen atom appear as a 4-proton multiplet between 2.96 and 2.86 ppm in the P.M.R. spectrum.

A series of decoupling experiments, summarised in Table 1, establishes that the $-C_7H_{11}O$ part is present as 2-methylcyclohexanone.

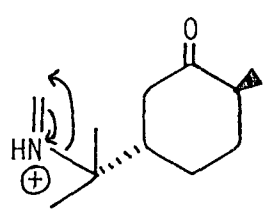
In the P.M.R. spectrum of fruticosonine, the single methyl group appears at 0.98 ppm as a doublet (J = 6.5 Hz) and is coupled to a methine proton ($H\text{-}C_{17}$) resonating at 2.19 ppm. This methine proton also shows a *trans*-diaxial coupling of 13.0 Hz with a proton ($H_{ax}\text{-}C_{18}$) on the adjacent carbon. The latter proton, which resonates at 1.16 ppm, is geminally coupled to the proton ($H_{eq}\text{-}C_{18}$) at 1.95 ppm, and both of

Scheme 1

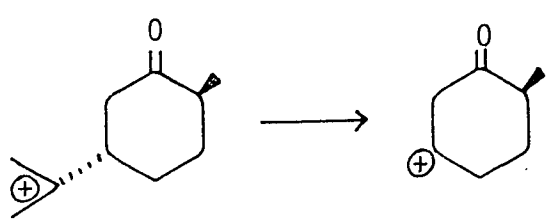


II $M^{+\cdot}$ (m/e 312)

α-cleavage

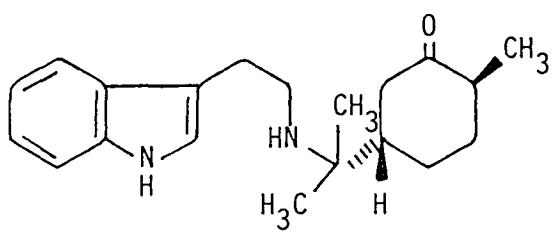


m/e 182



m/e 153 m/e 111

these are again coupled to another pair of methylene protons with signals at 1.63 (H_{eq}-C_{19}) and 1.13 ppm (H_{ax}-C_{19}). The last pair of methylene protons are also coupled to a methine proton (H-C_{14}) at 1.76 ppm which in turn is coupled to a third pair of geminal protons resonating at 2.34 (H_{eq}-C_{15}) and 2.03 ppm (H_{ax}-C_{15}). The H_{ax}-C_{19} proton shows *trans*-diaxial couplings of 13.0 Hz each with both H-C_{14} and H_{ax}-C_{18} protons. Similarly, the H-C_{14} proton also shows two large *trans*-diaxial couplings, each of 13.0 Hz, with the H_{ax}-C_{19} and H_{ax}-C_{15} protons.

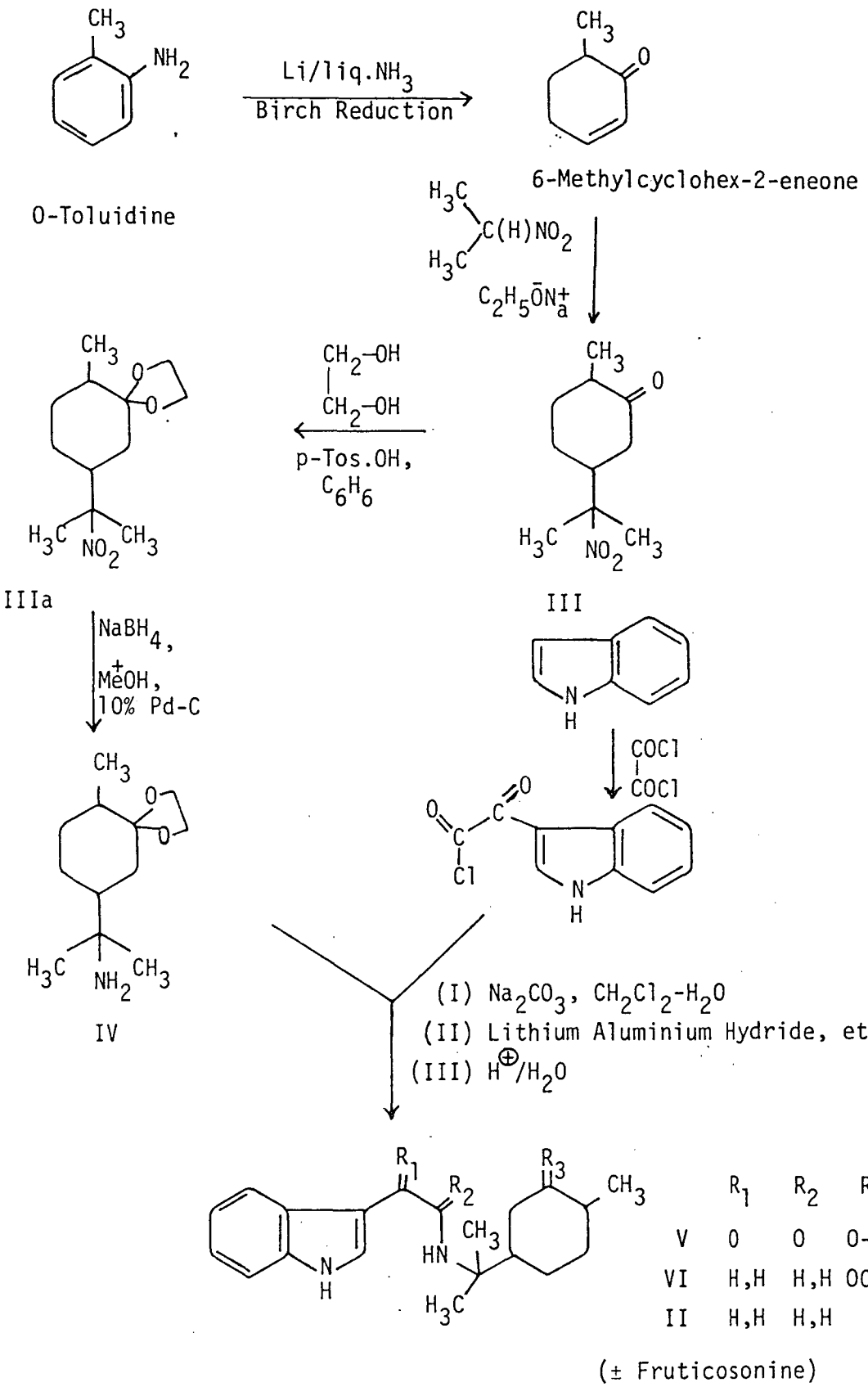


II

These spectroscopic data point to the structure (II) for fruticosonine, and this has been confirmed by X-ray crystallography, which also established the relative stereochemistry.[1] Crystal data: $C_{20}H_{28}N_2O$, M 312.5, tetragonal, a = 8.847(2), c = 47.857(9) Å; D_m = 1.12(2), D_c = 1.108 g cm^{-3}, Z = 8, space group $P4_32_12$, $F(1000)$ = 1360. The X-ray crystallographic structure is shown in Figure 3.

Racemic fruticosonine was synthesised by the route shown in Scheme 2. Racemic 6-methylcyclohex-2-ene was prepared from O-toluidine by Birch reduction following the method of White.[2] A Michael condensation of 2-nitropropane with 6-methylcyclohex-2-ene afforded an adduct (III) as a major product together with a minor component, possibly a diastereoisomer of (III). The mixture was separated by a short column of silica gel G_1 and eluted with pure chloroform. The

Scheme 2



	R_1	R_2	R_3
V	O	O	$O\text{-}CH_2\text{-}CH_2\text{-}O$
VI	H,H	H,H	OCH_2CH_2O
II	H,H	H,H	O

(± Fruticosonine)

carbonyl group of compound (III) was protected by the formation of an ethylene ketal followed by reduction of the nitro-group with sodium borohydride in the presence of 10% palladium on carbon to an amine (IV). 3-Indolyloxalyl chloride was prepared by the reaction of indole with oxalyl chloride in anhydrous ether,[5] and was reacted with the amine (IV) in a 1:1 mixture of dichloromethane and water in the presence of sodium carbonate. The addition product (V) was purified by preparative thin-layer chromatography (5% MeOH/$CHCl_3$), and reduced with lithium aluminium hydride to the base (VI), which was subsequently hydrolysed to give (±)-fruticosonine (II) in about 30% overall yield. The $R_{f's}$, infrared, ultraviolet and P.M.R. (Figure 4) spectra of both the natural and the synthetic fruticosonine were found to be identical.

2. Aristofruticosine

Aristofruticosine is shown to be an isomer of peduncularine[3] from its molecular formula, $C_{20}H_{24}N_2$, established by high-resolution mass spectrometry. However, the P.M.R. and ^{13}C N.M.R. spectra show that aristofruticosine has only one unit of unsaturation apart from the indole nucleus, the presence of which is indicated by the ultraviolet absorption spectrum (Figure 6). The P.M.R. spectrum shows a one-proton singlet at 6.93 ppm which can be assigned to the 2'-position of the indole nucleus. That this 2'-position is unsubstituted is confirmed by a positive Ehrlich test and by the presence of a strong m/e 130 ion peak, accompanied by its complementary peak at m/e 162 (base peak) in the mass spectrum. Thus it appears that the non-indolic portion of the structure of aristofruticosine comprises a three-ring system connected to the 3'-position of the indole nucleus through a methylene group.

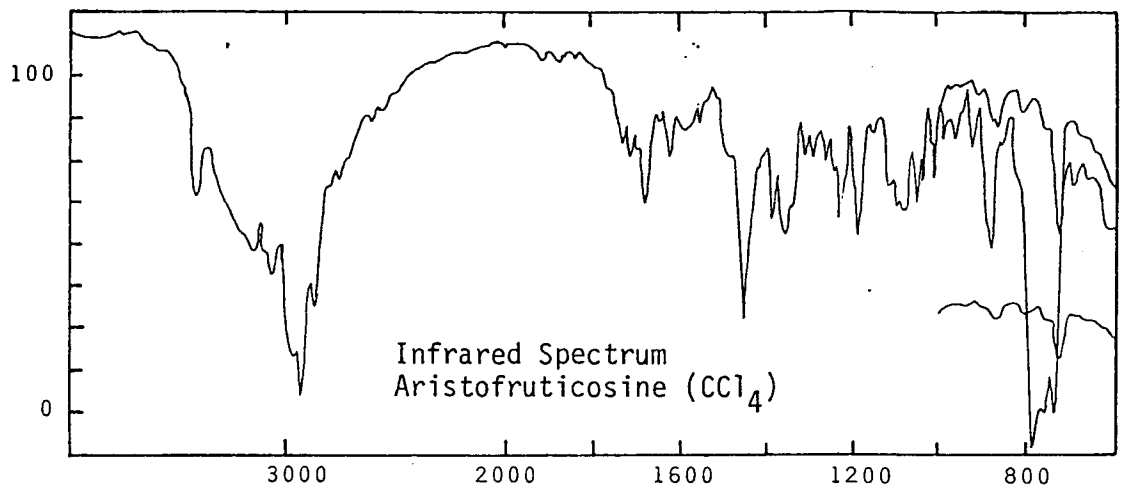


Figure 5.

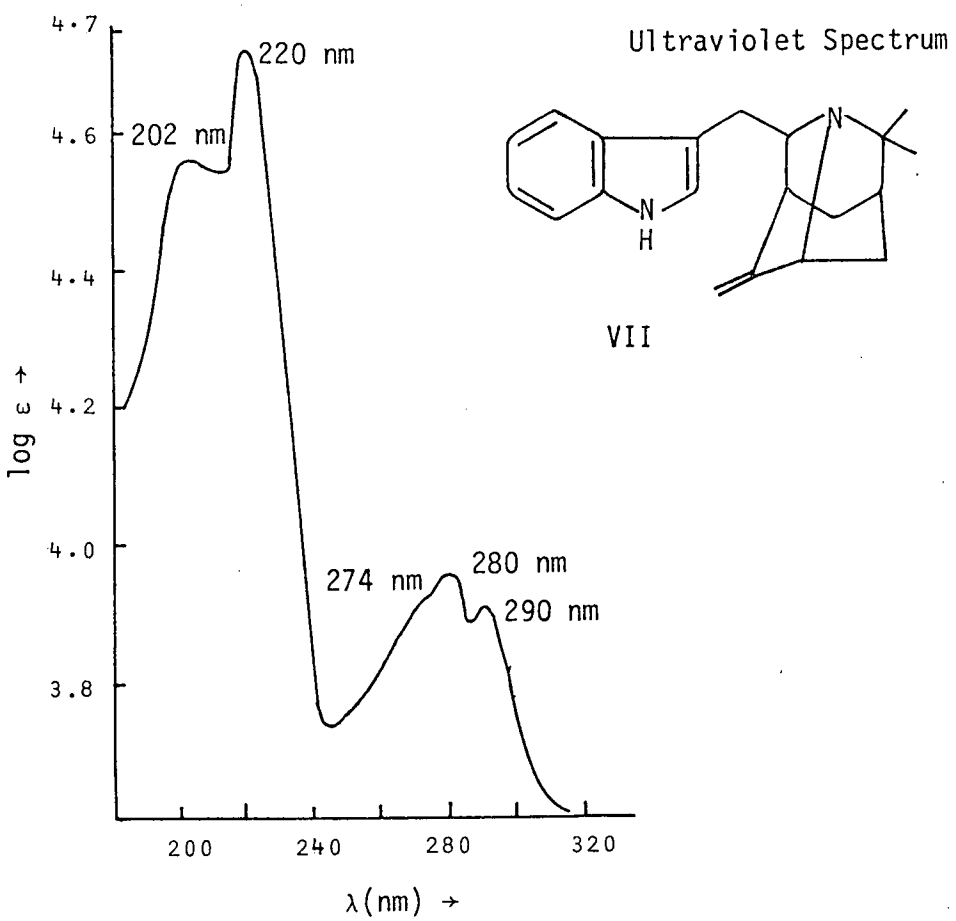
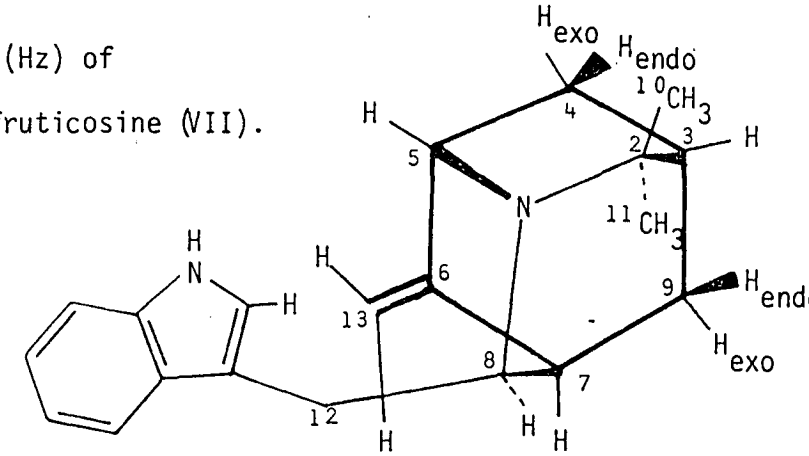


Figure 6.

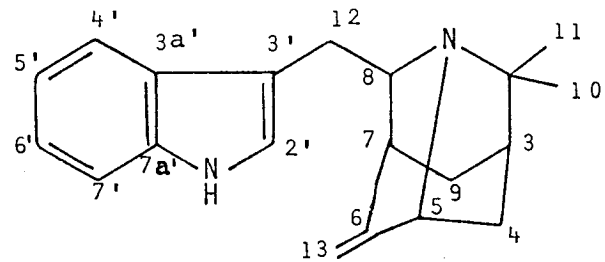
Table II. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of aliphatic and olefinic protons in the pmr spectrum of Aristofruticosine (VII).



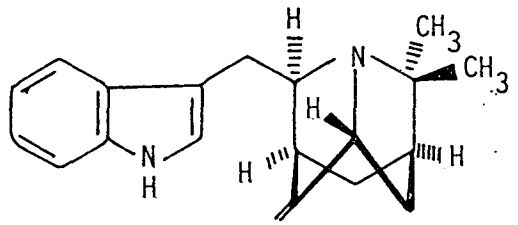
Protons	H_a-C_{12}	H_b-C_{12}	H-C_8	H-C_7	H_{endo}-C_9	H_{exo}-C_9	H-C_3	H_{endo}-C_4	H_{exo}-C_4	H-C_5	H_a-C_{13}	H_b-C_{13}	Multiplicities	Chemical shifts
H_a-C_{12}		14.0	5.0										dxd	2.82
H_b-C_{12}	14.0		10.0										dxd	2.66
H-C_8	5.0	10.0											dxd	3.6-
H-C_7					2.5	2.5							t	2.26
H_{endo}-C_9				2.5		13.0	2.5						dxt	1.47
H_{exo}-C_9				2.5	13.0		2.5	2.5					dxqa	1.95
H-C_3					2.5	2.5		2.5					qa	1.87
H_{endo}-C_4						2.5	2.5		12.0	7.0			dxdxt	2.50
H_{exo}-C_4								12.0					d	1.71
H-C_5								7.0			.44	.44	dxt	3.97
H_a-C_{13}										.44		.64	dxd	4.83
H_b-C_{13}										.44	.64		dxd	4.72

Table III

C-13 Chemical shifts of Aristofruticosine (measured in $CDCl_3$)



Carbon	2'	3'	3a'	4'	5'	6'	7'	7a'	2	3	7	4	5	6	8	9	12	10	11	13
δ TMS ppm	122.2	113.3	127.8	119.1	121.8	119.2	111.1	136.4	66.3	44.9	43.0	42.9	64.9	158.2	62.5	33.8	30.5	30.4	23.9	99.4
multiplicity	d	s	s	d	d	d	d	s	s	d	d	t	d	s	d	t	t	qa	qa	t



VII

The sequence of the remaining aliphatic protons has been established by a series of decoupling experiments, the results of which are presented in Table II.

The methylene proton signals (H_a, H_b-C_{12}) mentioned above appear at 2.82 and 2.66 ppm and show a large geminal coupling of 14.0 Hz. Each of these protons is again coupled to a methine proton (H-C_8) which resonates at 3.60 ppm and shows no other coupling. From its chemical shift, the methine proton can be assigned to a carbon α- to the non-indolic nitrogen. There is another low field proton (H-C_5) which resonates at 3.97 ppm and shows small allylic couplings with a pair of olefinic protons (H_a, H_b-C_{13}) appearing at 4.83 and 4.72 ppm. The fact that these olefinic protons are present in a vinylidine group is confirmed by the presence of a triplet at 99.4 ppm in the ^{13}C N.M.R. spectrum of aristofruticosine.

The aliphatic nitrogen is tertiary, and it appears likely that it is linked to C-5, since the proton attached to the latter resonates at 3.97 ppm. This proton shows coupling with another proton (H_{endo}-C_4) at 2.50 ppm ($J_{5/4endo}$ = 7.0 Hz). The latter proton is geminally coupled (J_{gem} = 12.0 Hz) to a proton (H_{exo}-C_4) at 1.71 ppm, and it also shows a small coupling with a methine proton (H-C_3) at 1.87 ppm; this

in turn is coupled to a pair of geminal protons appearing at 1.47 (H_{endo}-C_9) and 1.95 ppm (H_{exo}-C_9) (J_{gem} = 13.0 Hz). Each of these geminal protons is again coupled to another methine proton (H-C_7) appearing at 2.26 ppm as a triplet. The proton at 1.71 ppm (H_{exo}-C_4) shows no other couplings and the dihedral angles between it and each of the protons at 1.87 (H-C_3) and 3.97 ppm (H-C_5) appear to be 90°. However, there is a 4-bond coupling (J = 2.5 Hz) between the H_{endo}-C_4 and the H_{exo}-C_9 protons. The two methine protons at 3.60 (H-C_8) and 2.26 ppm (H-C_7) show no mutual coupling, and the dihedral angle in this case also appears to be 90°.

The spectroscopic data point to a structure (VII) for aristofruticosine, with the relative stereochemistry shown.

All the carbons in structure (VII) can be accounted for in the ^{13}C N.M.R. spectrum. The chemical shifts, multiplicities and assignments are presented in Table III.

3. Isopeduncularine

Isopeduncularine has also been isolated as a minor base from *A. serrata*. From the molecular formula $C_{20}H_{24}N_2$, which was established by high-resolution mass spectrometry and confirmed by analysis, it is isomeric with peduncularine[3] (IX). The ultraviolet absorption spectrum (Figure 8) indicates that isopeduncularine has an indole nucleus present. The single proton doublet at 6.96 ppm in the P.M.R. spectrum together with a singlet at 122.1 ppm in the ^{13}C N.M.R. spectrum suggests that the 2'-position of the indole nucleus is free. This inference has been confirmed by a positive Ehrlich test and also by the presence of a strong m/e 130 peak in the mass spectrum of isopeduncularine.

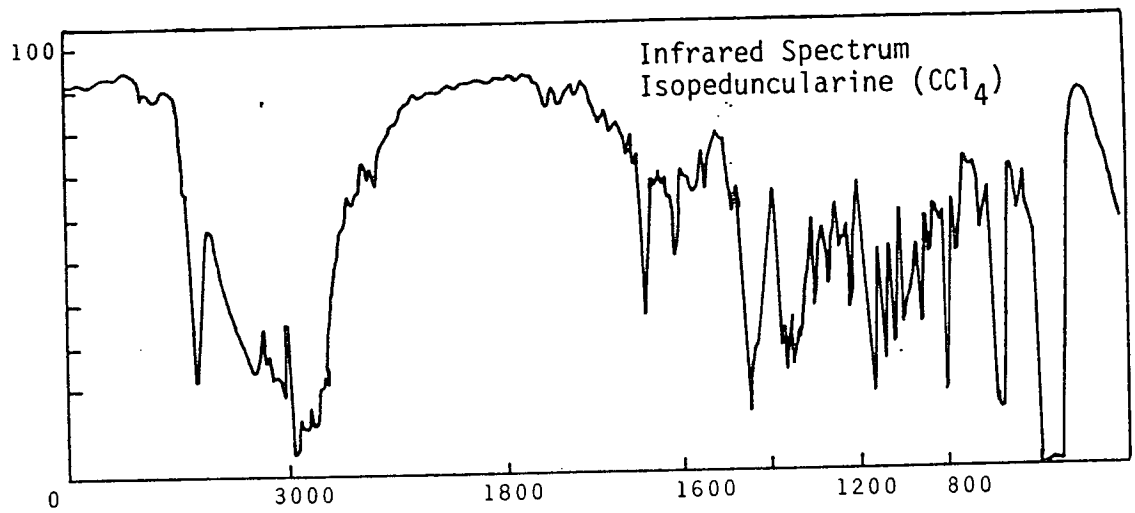
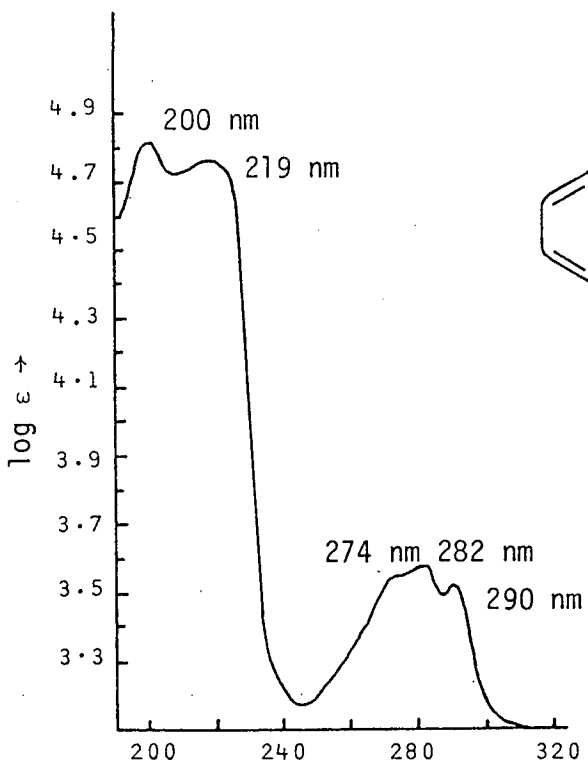
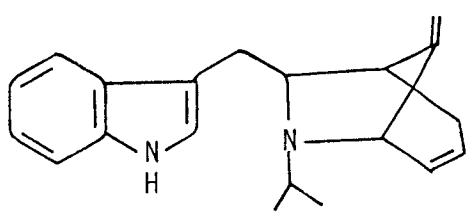


Figure 7.

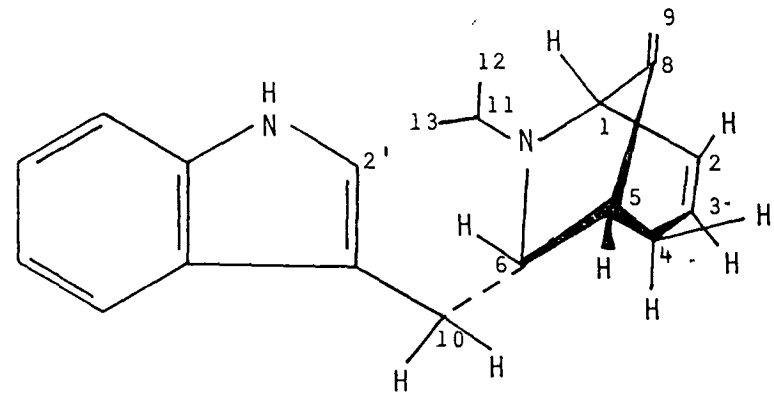




VIII

Figure 8.

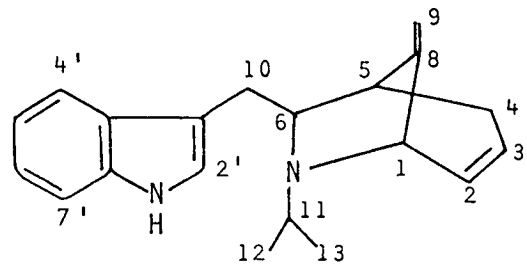
Table IV. Chemical shifts (ppm), multiplicities and coupling constants (Hz) of the aliphatic and olefinic protons in the pmr spectrum of Isopeduncularine (VIII).



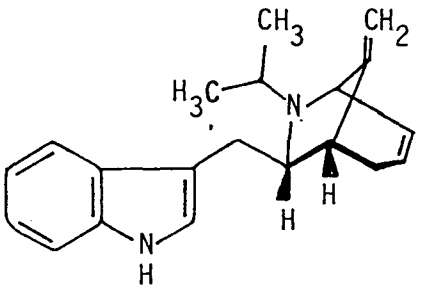
Protons	H_a-C(10)	H_b-C(10)	H-C(6)	H-C(5)	H_{exo}-C(4)	H_{endo}-C(4)	H-C(3)	H-C(2)	H-C(1)	Multiplicities	Chemical shifts
H_a-C(10)											
H_b-C(10)	15.0		10.5							dxd	2.72
H-C(6)											
H-C(5)										m	2.50
H_{exo}-C(4)				5.0		19.0	3.0	2.0		dxdxdxd	2.47
H_{endo}-C(4)				<1	19.0		2.5	2.0		dxdxdxd	2.04
H-C(3)					3.0	2.5		9.5		dxdxd	5.67
H-C(2)					2.0	2.0	9.5		5.1	dxdxt	5.93
H-C(1)								5.1		d	3.86

Table V

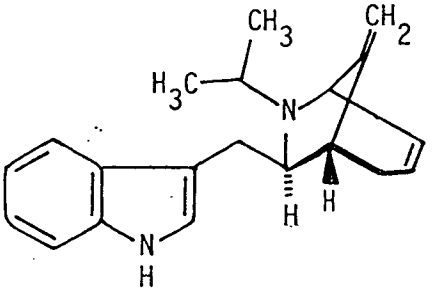
C-13 Chemical shifts of Isopeduncularine (measured in $CDCl_3$)



Carbon	2'	3'	3a'	4'	5'	6'	7'	7a'	1	2	3	4	5	6	8	9	10	11	12	13
δ^{TMS}_{ppm}	122.1	114.8	127.7	119.2	121.5	119.5	111.1	136.2	70.1	130.9	128.5	34.2	46.2	60.7	149.7	101.2	40.3	51.0	23.6	22.7
Multiplicity	d	s	s	d	d	d	d	s	d	d	d	t	d	d	s	t	t	d	qa	qa



VIII

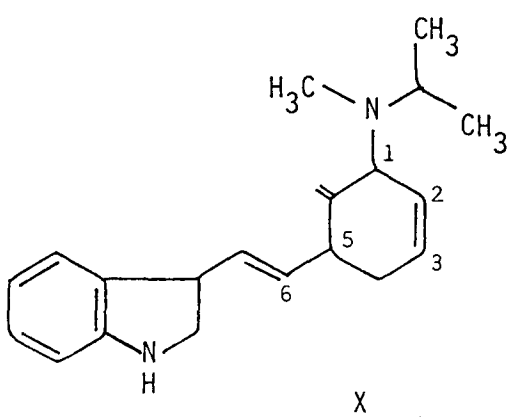


IX

The P.M.R. spectrum of isopeduncularine contains signals for four olefinic protons, two of which appear to be in a vinylidine group. The presence of this group is confirmed by a methylene carbon signal at 101.2 ppm in the ^{13}C P.M.R. spectrum. The strong ion peaks at m/e 130 and m/e 162 (base peak) present in the mass spectrum of isopeduncularine suggest that the non-indolic part of the molecule is connected to the 3'-position of the indole nucleus through a $-CH_2-$ group. The appearance of two sets of 3-proton doublets (J = 6.5 Hz) centred at 1.32 and 1.17 ppm indicates the presence of an isopropyl group. As in the case of peduncularine, this group is possibly attached to the aliphatic nitrogen, which appears to be tertiary. This inference has been supported by the presence of a M-15 peak in the mass spectrum of isopeduncularine.

A series of decoupling experiments, presented in Table IV, and ^{13}C data (Table V) points to the same skeleton (VIII) for isopeduncularine as has been established for peduncularine.[3] The methine proton on C-1 appears as a doublet centred at 3.86 ppm and is coupled to the adjacent olefinic proton $H-C_2$ (J = 5.1 Hz). There is a *cis*-vicinal coupling of 9.5 Hz between the two olefinic protons $H-C_2$ and $H-C_3$, both of which are weakly coupled to a pair of geminal protons ($2H-C_4$, J_{gem} = 19.0 Hz). One ($H_{exo}-C_4$) of these geminal

protons also show a medium coupling of 5.0 Hz with an adjacent methine proton (H-C_5) the signal of which appears at 2.50 ppm, whereas the other geminal proton (H_{endo}-C_4) shows a small (<1 Hz) coupling with the H-C_5 proton, indicating a dihedral angle close to 90°. On decoupling the H_{endo}-C_4 proton (2.04 ppm), the splitting pattern of the H-C_5 signal is changed into a doublet of a doublet, thus indicating a possible coupling with the H-C_6 proton. The P.M.R. spectrum of isopeduncularine shows no allylic couplings between the methine proton (H-C_5) and the vinylidine protons ($H_{a,b}$-C_9). The methine proton H-C_6 could not be decoupled because its signal was overlapped with those of two other protons H_a-C_{10} and H-C_{11}. Thus isopeduncularine possibly differs from peduncularine in having a coupling between the two adjacent methine protons H-C_6 and H-C_5.* Moreover, in contrast to peduncularine, isopeduncularine is readily soluble in chloroform, from which it was eventually crystallised with a m.p. of 113-114°C as compared to 155-157°C in the case of peduncularine. A mixed melting-point of the two samples showed a depression of 3-4°C. Another distinct difference is in their optical rotations: isopeduncularine has $[\alpha]_D^{19}$ - 40° ($CHCl_3$) as compared to $[\alpha]_D^{19}$ - 76° ($CHCl_3$) for peduncularine. Their spectroscopic data are almost identical, which suggests that they form a pair of stereoisomers. Table VI shows the comparative chemical shift values of their protons and carbons.



X

*In peduncularine,[3] C-6 and C-5 protons are not coupled and have a dihedral angle of 90°.

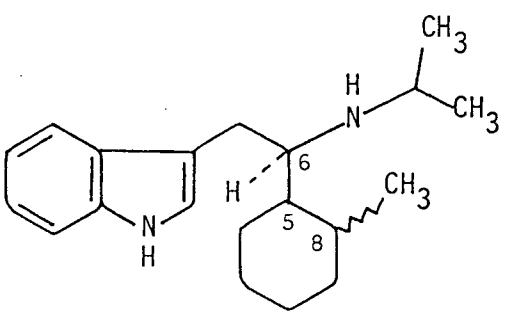
Table VI

Protons	Chemical Shifts (ppm) in Isopeduncularine	Peduncularine
$H\text{-}C_2'$	6.96	6.93
$2H\text{-}C_9$	4.96, 4.83	4.94, 4.81
$H\text{-}C_1$	3.86	3.85
$H\text{-}C_{11}$, $H\text{-}C_6$, $H_a\text{-}C_{10}$	3.06-2.89	3.1-2.85
$H_b\text{-}C_{10}$	2.72	2.65
$H\text{-}C_5$	2.50	2.49
$3H\text{-}C_{12}$ + $3H\text{-}C_{13}$	1.32, 1.17	1.32, 1.17

C-13 Chemical Shifts (ppm)

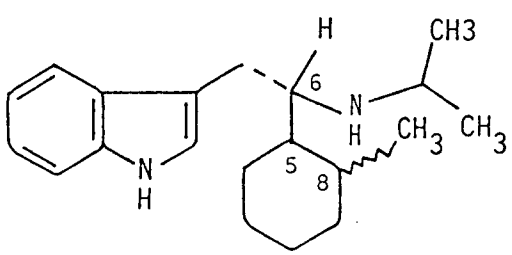
Carbon	Isopeduncularine	Peduncularine
8	149.7	149.8
7a'	136.2	136.1
2,3	130.9, 128.5	130.4, 128.4
3a'	127.7	127.7
2', 4', 5', 6'	122.1, 121.5, 119.5, 119.2	121.8, 121.3, 119.1, 119.0
3'	114.8	114.8
7'	111.1	110.9
9	101.2	101.3
1	70.1	69.9
6	60.7	60.4
11	51.0	50.9
5	46.2	45.9
10	40.3	40.1
4	34.2	34.2
12,13	23.6, 22.7	23.6, 22.7

The Hofmann degradation products from peduncularine and isopeduncularine have been found to be identical (X). On catalytic hydrogenation, a mixture of two products was obtained from each of peduncularine and isopeduncularine. The formation of two isomers can be explained by the introduction of a new chiral centre: there were originally three asymmetric carbons present in the moleculesof both peduncularine and isopeduncularine; on hydrogenation, the asymmetry around one carbon (C-1) is lost, but a new chiral centre (C-8) is formed. A difference in stereochemistry around C-5 in each case can be excluded on the grounds that C-5 forms a bridgehead. There remains the possibility of a difference in stereochemistry around C-6. This hypothesis is supported by the isolation of two other pairs of isomers (hobartine-isohobartine and sorelline-isosorelline), which likewise appear to be epimeric at the same carbon.



XI, XII

epimeric at C-8



XIII, XIV

epimeric at C-8

Finally, the hydrogenolysed products (XI, XII) from isopeduncularine have proved to be different to those (XIII, XIV) from peduncularine, and on this basis the structure (VIII) is proposed for isopeduncularine.

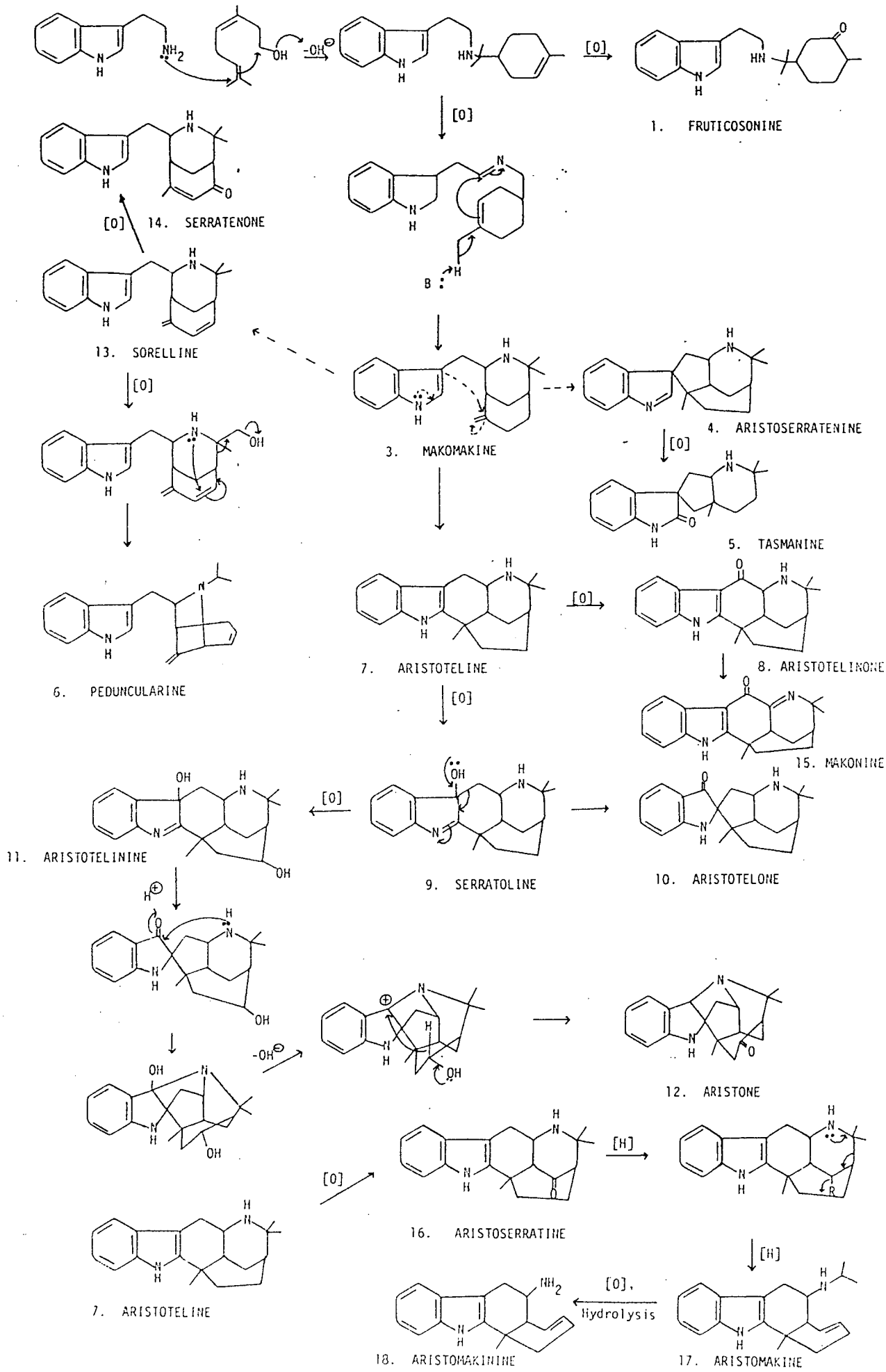
Biogenesis of *Aristotelia* Alkaloids

Aristotelia alkaloids comprise a group of about twenty known bases, and form a completely new series of indole alkaloids. The first member of the group, peduncularine,was reported in 1971. Although no labelling experiments have yet been carried out to establish the biogenetic pathway to these alkaloids, several suggestions[6-8] have already been made.

Despite the isolation of several different structural types within this small group of alkaloids, most of these types have a number of features in common, e.g. i) twenty carbons (except in aristomakinine) and two nitrogen atoms, ii) a geminal dimethyl group, iii) an extra methyl group (except in peduncularine (6), isopeduncularine and makomakine (3)). Base on these features, a preliminary communication[6] suggested a possible biogenetic pathway to these alkaloids, in accordance with which *Aristotelia* alkaloids originate in a tryptamine and a monoterpene unit. In contrast to other groups of indole alkaloids, the terpene unit, possibly geraniol, is incorporated without rearrangement into the structure of most of these *Aristotelia* alkaloids. However, in the case of peduncularine (6) and isopeduncularine, the isopropyl group is transferred from the terpene unit to the non-indolic nitrogen; this probably applies in the case of aristomakine (17) as well.

Several compounds such as (3), (4), (9), (13), which appeared as hypothetical intermediates in the biogenetic scheme 4 proposed initially have since been isolated. These include the key intermediate (3), subsequently named makomakine after its isolation from *A. serrata*.

The only C-17 *Aristotelia* alkaloid, aristomakinine (18) has recently been isolated. Aristomakinine lacks an isopropyl group as compared to aristomakine(17), from which it may possibly be formed by an α-oxidation adjacent to the non-indolic nitrogen followed by hydrolysis, which would result in the removal of the isopropyl group.


[O]
1. FRUTICOSONINE
[O]
14. SERRATENONE
13. SORELLINE
[O]
3. MAKOMAKINE
4. ARISTOSERRATENINE
[O]
5. TASMANINE
6. PEDUNCULARINE
7. ARISTOTELINE
[O]
8. ARISTOTELINONE
15. MAKONINE
[O]
11. ARISTOTELININE
9. SERRATOLINE
10. ARISTOTELONE
12. ARISTONE
[O]
16. ARISTOSERRATINE
[H]
[H]
[O], Hydrolysis
18. ARISTOMAKININE
17. ARISTOMAKINE
7. ARISTOTELINE

Scheme 4

3.II. EXPERIMENTAL

1. Extraction procedure

Roots, stems and leaves of *Aristotelia fruticosa* collected from Rotorua, New Zealand were air-dried, ground to a fine powder (1.7 Kg) in a Wiley mill, and exhaustively extracted with methanol at room temperature until a test sample gave a negative Mayer's test. The extract was concentrated *in vacuo* at a temperature below 40°C to a thick gummy dark brown concentrate which was dissolved in 500 ml of warm glacial acetic acid. The solution was poured in a fine stream into 7 ℓ of water with rapid agitation by means of a vibromixer. The solution was left to stand overnight and the precipitate that settled out was filtered off and washed with water several times until free from alkaloids. The solution and washings were combined and evaporated almost to dryness *in vacuo*. The residue was treated with more water and the mixture evaporated again. The operation was repeated once more to get rid of most of the acetic acid, and finally the residue was treated with 1.5 ℓ of water. The mixture was basified to pH 8 with ammonia (d, 0.88) and extracted with chloroform (250 ml x 5). The combined chloroform extracts were thoroughly extracted with 5% (w/v) sulphuric acid (200 ml x 6). The aqueous acid solution was basified with ammonia (d, 0.88) and thoroughly extracted with chloroform (200 ml x 6). The combined chloroform extracts were dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo* to give 367 mg (0.02%) of crude alkaloids.

2. Separation and characterisation of the Alkaloids

Analytical t.l.c. (silica gel - 0.5 N KOH, 5% EtOH/$CHCl_3$) revealed the presence of one major and at least four minor components. P.t.l.c. on a 1-metre plate coated with silica gel prepared with 0.5 N KOH, using 5% EtOH/$CHCl_3$ as the solvent system, separated the mixture into four bands. The highest R_f band was extracted to give 90 mg of the major alkaloid, isopedundularine, which gave a positive Ehrlich test. It crystallised from chloroform as colourless needles, m.p. 113-114°C, $[\alpha]_D^{19}$ -40° (C, 4.1, $CHCl_3$), $[\alpha]_D^{19}$ -45° (C, 4.1, MeOH); λ_{max} (MeOH): 290 nm (3.52), 282 nm (3.57), 274 nm (sh, 3.55), 219 nm (4.76), 200 nm (4.82); ν_{max} (CCl_4): 3400 cm^{-1} (-NH), 1680 cm^{-1} (C=C); P.M.R. (δ ppm): 8.21 (1H, br. s, exchangeable with D_2O, H-N_a); 7.08-7.62 (4H, multiplets, aromatic protons); 6.96 (1H, d, J = 2.4 Hz, H-$C_{2'}$); 5.93 (1H, ddt, $J_{2/3}$ = 9.5 Hz, $J_{2/1}$ = 5.1 Hz, $J_{2/4exo,4endo}$ = 2.0 Hz, H-C_2); 5.67 (1H, ddd, $J_{3/2}$ = 9.5 Hz, $J_{3/4exo}$ = 3.0 Hz, $J_{3/4endo}$ = 2.5 Hz, H-C_3); 4.96 and 4.83 (2 x 1H, 2s, 2H-C_9); 3.86 (1H, d, $J_{1/2}$ = 5.1 Hz, H-C_1); 3.06-2.89 (3H, multiplets, H-C_6 + H-C_{11} + H_a - C_{10}); 2.72 (1H, dd, $J_{10b/10a}$ = 15.0 Hz, $J_{10b/6}$ = 10.5 Hz, H_b-C_{10}); 2.50 (1H, m, H-C_5); 2.47 (1H, dddd, $J_{4exo/4endo}$ = 19.0 Hz, $J_{4exo/5}$ = 5.0 Hz, $J_{4exo/3}$ = 3.0 Hz, $J_{4exo/2}$ = 2.0 Hz, H_{exo}-C_4); 2.04 (1H, dddd, $J_{4endo/4exo}$ = 19.0 Hz, $J_{4endo/3}$ = 2.5 Hz, $J_{4endo/2}$ = 2.0 Hz, H_{endo}-C_4); 1.32 and 1.17 (3H x 2, 2d, J = 6.5 Hz, 3H-C_{12} + 3H-C_{13}). H.R.M.S.: m/e 292 ($M^{+\cdot}$, 2). Meas.: 292.1931; calc. for $C_{20}H_{24}N_2$: 292.1939, 277 (<1%), 182 (1.5), 163 (7), 162 (100), 130 (5), 120 (7), 105 (4), 103 (3), 91 (8), 70 (6). ^{13}C N.M.R. (δ_{ppm}^{TMS}): 149.7 (s, C-8); 136.2 (s, C-$7_{a'}$); 130.9 + 128.5 (2d, C-2 + C-3); 127.7 (s, C-$3_{a'}$); 122.1 (d, C-2'); 121.5 (d, C-5'); 119.5 (d, C-6'); 119.2 (d, C-4'); 114.8 (s, C-3'); 111.1 (d, C-7'); 101.2 (t, C-9); 70.1 (d, C-1);

60.7 (d, C-6); 51.0 (d, C-11); 46.2 (d, C-5); 40.3 (t, C-10); 34.2 (t, C-4); 23.6 + 22.7 ($2q_a$, C-12 + C-13). Analysis: C, 66.83; H, 6.60; N, 7.34. Calc. for $C_{20}H_{24}N_2$, $CHCl_3$: C, 67.00; H, 6.70; N, 7.44.

From the second R_f band a new alkaloid (33.5 mg), named fruticosonine, was isolated. It gave a positive Ehrlich test, and crystallised from ether to give colourless square prisms, m.p. 120-121°C, $[\alpha]_D^{20}$ + 45.7° (C, 0.48, $CHCl_3$), λ_{max} (MeOH): 290 nm (3.72), 282 nm (3.79), 275 nm (sh, 3.76), 223 nm (4.45); ν_{max} (Nujol): 3400 cm^{-1} (-NH), 3280 cm^{-1} (-NH), 1710 cm^{-1} (s, >C=O); P.M.R. (δ ppm): 8.25 (1H, broad, exchangeable with D_2O, H-N_a); 7.62-7.08 (4H, multiplets, 4 aromatic protons); 7.02 (1H, d, J = 1.7 Hz, H-$C_{2'}$); 2.96-2.86 (4H, multiplets, 2H-C_{10} + 2H-C_{11}); 2.34 (1H, dd, $J_{15eq/15ax}$ = 13.0 Hz, $J_{15eq/14}$ = 3.5 Hz, H_{eq}-C_{15}); 2.19 (1H, dq_a, $J_{17/18ax}$ = 13.0 Hz, $J_{17/20}$ = 6.5 Hz, H-C_{17}); 2.03 (1H, t, $J_{15ax/15eq,14}$ = 13.0 Hz, H_{ax}-C_{15}); 1.95 (1H, dt, $J_{18eq/18ax}$ = 13.0 Hz, $J_{184q/19ax,19eq}$ = 3.5 Hz, H_{eq}-C_{18}); 1.76 (1H, tt, $J_{14/15ax,19ax}$ = 13.0 Hz, $J_{14/15eq,19eq}$ = 3.5 Hz, H-C_{14}); 1.63 (1H, dq_a, $J_{19eq/19ax}$ = 13.0 Hz, $J_{19eq/14,18eq,18ax}$ = 3.5 Hz, H_{eq}-C_{19}); 1.33 (1H, qad, $J_{19ax/18ax,14,19eq}$ = 13.0 Hz, $J_{19ax/18eq}$ = 3.5 Hz, H_{ax}-C_{19}); 1.16 (1H, qad, $J_{18ax/18eq,19ax,17}$ = 13.0 Hz, $J_{18ax/19eq}$ = 3.5 Hz, H_{ax}-C_{18}); 1.3-1.0 (1H, broad, exchangeable with D_2O, H-N_b); 0.99 (6H, s, 3H-C_{21} + 3H-C_{22}); 0.98 (3H, d, $J_{20/17}$ = 6.5 Hz, 3H-C_{20}). High Resolution Mass Spec.: m/e 312 (M^+, <2%), 238 (<2); 201 (80, $C_{13}H_{17}N_2$), 182 (100, $C_{11}H_{20}NO$), 153 (23, $C_{10}H_{17}O$), 144 (72, $C_{10}H_{10}N$), 130 (45, C_9H_8N), 83 (17, C_6H_{11}). Analysis: Found: C, 76.61; H, 9.11; N, 8.90. $C_{20}H_{28}N_2O$ requires: C, 76.88; H, 9.03; N, 8.96.

Another new alkaloid, aristofruticosine, which gave a positive Ehrlich test, was isolated from the third R_f band (30 mg). It could not be crystallised from any solvent, but had $[\alpha]_D^{15}$ + 50.5° (C, 0.55,

$CHCl_3$); λ_{max} (MeOH): 290 nm (3.91), 280 nm (3.96), 274 nm (sh, 3.94), 220 nm (4.72), 202 nm (4.56); ν_{max} (CCl_4): 3400 cm^{-1} (-NH), 1680 cm^{-1} (w, >C=C<); P.M.R. (δ ppm): 8.3 (1H, broad, exchangeable with D_2O, $H\text{-}N_a$); 7.7-7.1 (4H, multiplets, aromatic protons); 6.93 (1H, s, $H\text{-}C_{2'}$); 4.83 (1H, dd, $J_{13a/13b}$ = 0.64 Hz, $J_{13a/5}$ = 0.44 Hz, $H_a\text{-}C_{13}$); 4.72 (1H, dd, $J_{13b/13a}$ = 0.64 Hz, $J_{13b/5}$ = 0.44 Hz, $H_b\text{-}C_{13}$); 3.97 (1H, dt, $J_{5/4endo}$ = 7.0 Hz, $J_{5/13a,13b}$ = 0.44 Hz, $H\text{-}C_5$); 3.60 (1H, dd, $J_{8/12b}$ = 10.0 Hz, $J_{8/12a}$ = 5.0 Hz, $H\text{-}C_8$); 2.82 (1H, dd, $J_{12a/12b}$ = 14.0 Hz, $J_{12a/8}$ = 5.0 Hz, $H_a\text{-}C_{12}$); 2.66 (1H, dd, $J_{12b/12a}$ = 14.0 Hz, $J_{12b/8}$ = 10.0 Hz, $H_b\text{-}C_{12}$); 2.50 (1H, ddt, $J_{4endo/4exo}$ = 12.0 Hz, $J_{4endo/5}$ = 7.0 Hz, $J_{4endo/9exo,3}$ = 2.5 Hz, $H_{endo}\text{-}C_4$); 2.26 (1H, t, $J_{7/9exo,9endo}$ = 2.5 Hz, $H\text{-}C_7$); 1.95 (1H, dqa, $J_{9exo/9endo}$ = 13.0 Hz, $J_{9exo/7,3,4endo}$ = 2.5 Hz, $H_{exo}\text{-}C_9$); 1.87 (1H, qa, $J_{3/9exo,9endo,4endo}$ = 2.5 Hz, $H\text{-}C_3$); 1.71 (1H, d, $J_{4exo/4endo}$ = 12.0 Hz, $H_{exo}\text{-}C_4$); 1.47 (1H, dt, $J_{9endo/9exo}$ = 13.0 Hz, $J_{9endo/7,3}$ = 2.5 Hz, $H_{endo}\text{-}C_9$); 1.44 and 1.15 (2 x 3H, 2s, $3H\text{-}C_{10}$ + $3H\text{-}C_{11}$). H.R.M.S.: m/e 292 ($M^{+\cdot}$, 72). Meas.: 292.1929; calc. for $C_{20}H_{24}N_2$: 292.1939; 277 (22, $C_{19}H_{21}N_2$); 249 (5); 199 (7); 162 (100, $C_{11}H_{16}N$); 130 (37, C_9H_8N); 120 (16, $C_8H_{10}N$); 93 (15), 91 (15, C_7H_7). ^{13}C N.M.R. (δ^{TMS}_{ppm}): 158.2 (s, C-6); 136.4 (s, C-7a'); 127.8 (s, C-3a'); 122.2 (d, C-2'); 121.8 (d, C-5'); 119.2 (d, C-6'); 119.1 (d, C-4'); 113.3 (s, C-3'); 111.1 (d, C-7'); 99.4 (t, C-13); 66.3 (s, C-2); 64.9 (d, C-5); 62.5 (d, C-8); 44.9 and 43.0 (2d, C-7 + C-3); 42.9 (t, C-4); 33.8 and 30.5 (2t, C-9 + C-12); 30.4 and 23.9 (2qa, C-10 + C-11).

From the fourth (lowest) R_f band was isolated 15 mg of a mixture of alkaloids, which from analytical t.l.c. (silica gel - 0.5 N KOH, 20% EtOH/$CHCl_3$) had two components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N, KOH, 20% EtOH/$CHCl_3$). The higher R_f band was extracted to give 4 mg of isosorelline, whose identity was

established by direct comparison of [α], m.p., R_f, u.v., i.r., p.m.r. and mass spectra with a sample of isosorelline isolated from *A. serrata*.

The lower R_f band provided 3 mg of another alkaloid which had identical [α], t.l.c., m.p., and spectroscopic data (u.v., i.r., p.m.r. and m.s.) to isohobartine isolated from *A. serrata*.

Hofmann degradation of isopeduncularine (VIII)

100 mg of (VIII) in nitromethane (5 ml) was treated with 0.5 ml of methyl iodide and the resulting solution was stirred at room temperature (19°C) for 10 hr. The solvent was then removed *in vacuo* and the gummy residue of isopeduncularine methiodide was converted into the methofluoride by ion exchange (CH_3OH/H_2O 1:1; Amberlite IRA-400 (F^-)). The residue was dissolved in methanol, distributed in 8 bulb tubes (≈ 5 ml), and the solvent was evaporated *in vacuo* so as to give a thin film of the compound on the internal surfaces. The material was then pyrolysed (metal bath 140-145°C, 1.0×10^{-3} mm/Hg). The clear brown distillates were dissolved in chloroform, combined and evaporated to give 47 mg of a residue. Purification by p.t.l.c. (cyclohexane:EtOAc:ether:NH_4OH 40:40:20:1) yielded 21 mg of an oil, $[\alpha]_D^{19}$ -12° (C, 0.32, MeOH); λ_{max} (MeOH): 297 nm (sh, 3.71), 280 nm (3.85), 258 nm (4.21), 252 nm (sh, 4.13), 224 nm (4.32); ν_{max} ($CHCl_3$): 3490 cm^{-1} (H-N), 1660 cm^{-1}; P.M.R. (δ ppm): 8.45 (1H, br. s, exchangeable with D_2O, H-N_a); 7.83 (1H, d); 7.3-7.1 (3H, multiplets); 6.7-6.28 (2H, multiplets); 5.92-5.70 (2H, multiplets); 5.30 (1H, s); 5.07 (1H, s); 4.03 (1H, br.s); 3.2-2.85 (2H, multiplets); 2.4-2.1 (5H, including N-CH_3); 1.08 + 1.06 (3H x 2, 2d, J = 6.0 Hz); M.S.: m/e 306 ($M^{\cdot+}$, 70); 291 (29); 235 (49), 234 (100), 233 (31), 232 (47), 220 (10), 219 (18), 218 (21), 207 (19), 180 (20), 144 (56), 143 (51),

130 (73), 118 (63).

The corresponding Hofmann degradation product from peduncularine had $[\alpha]_D^{19}$ - 14° (MeOH). It also had the same R_f and similar spectroscopic (i.r., u.v., p.m.r. and m.s.) properties with those of the product from isopeduncularine.

Hydrogenation of isopeduncularine (VIII)

100 mg of (VIII) was hydrogenated in 5 ml glacial acetic acid with H_2 and 25 mg PtO_2 for 20 hr at 19°C under 3 atmos. pressure. The catalyst was then filtered off, the solution was diluted with 10 ml water, made basic with ammonium hydroxide and extracted with chloroform (10 ml x 3). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 70 mg of a residue. Analytical t.l.c. (silica gel - 0.5 N KOH, 4% EtOH/$CHCl_3$) showed the presence of two components. The mixture was separated by p.t.l.c. (silica gel - 0.5 N KOH, 4% EtOH/$CHCl_3$, double development) into two bands. The higher R_f band was extracted to give 18.3 mg of a hydrogenolysed product which could not be crystallised, but had $[\alpha]_D^{19}$ + 53° (C, 0.30, MeOH); λ_{max} (MeOH): 290.5 nm (3.29), 282 nm (3.35), 274 nm (sh, 3.31), 228 nm (3.80); ν_{max} ($CHCl_3$): 3480 cm^{-1}, 3420 cm^{-1}; P.M.R. (δ ppm): 8.1 (1H, br.s, exchangeable with D_2O, H-N_a); 7.2-7.05 (4H, aromatic protons), 7.02 (1H, s, H-$C_{2'}$); 3.1-2.6 (4H, multiplets); 2.13 (1H, m); 1.76-1.2 (10H, multiplets); 0.98 + 0.95 + 0.85 (3H x 3, 3d, J = 6.5 Hz). M.S.: m/e 235 (21), 201 (64), 168 (100), 152 (10), 130 (66), 98 (41). The corresponding hydrogenolysed product from peduncularine has the same R_f value and similar spectroscopic properties (u.v., p.m.r., m.s.) but different $[\alpha]_D^{19}$ (+ 35°).

Extraction of the lower R_f band afforded 10.8 mg of another

hydrogenolysed product which crystallised from chloroform, on chilling, as colourless crystals, m.p. 116-120°C, $[\alpha]_D^{19}$ + 126° (C, 0.18, MeOH); λ_{max} (MeOH): 290.5 nm (3.34); 282 nm (3.39); 274 nm (sh, 3.36); 228 nm (3.77); ν_{max} ($CHCl_3$): 3475 cm^{-1}, 3410 cm^{-1}; P.M.R. (δ ppm): 8.15 (1H, br.s, exchangeable with D_2O, H-N_a); 7.6 (1H, m); 7.35-7.1 (3H, multiplets), 7.02, 1H, H-$C_{2'}$); 3.2 (1H, m), 3.03-2.8 (1H, m); 2.7-2.3 (2H, multiplets); 2.0-1.1 (11H, multiplets); 1.06 + 0.92 + 0.62 (3H x 3, 3d). M.S.: 201 (10), 168 (100), 130 (21), 72 (8). The corresponding hydrogenolysed product from peduncularine also crystallised from chloroform, on chilling, as colourless crystals, m.p. 106-110°C (m.m.p. 101-108°), $[\alpha]_D^{19}$ + 81° (C, 0.34, MeOH); λ_{max} (MeOH): 290.5 nm (3.05), 282 nm (3.11), 275 nm (sh, 3.08), 225.5 nm (3.55); ν_{max} ($CHCl_3$): 3475 cm^{-1}, 3400 cm^{-1} (finger-print regions in the i.r. spectra are different). They have the same R_f values and similar p.m.r. and mass spectra.

Synthesis of Fruticosonine

1. Preparation of 6-methyl-2-cyclohexen-1-one[2]

Lithium (2.8 g, 0.4 mole) was dissolved in 150 ml of liquid ammonia with stirring and a solution of o-toluidine (0.7 g, 0.10 mole) in 30 ml of dry tert.-butyl alcohol was stirred in during 5 min. The mixture was stirred until decolourisation (about 2 hr) and 250 ml of water was added cautiously. The aqueous solution was allowed to warm up to 25° and was extracted with ether (40 ml x 4). After removal of the ether and tert.-butyl alcohol *in vacuo*, 200 ml of ice-cold 5% (w/v) hydrochloric acid was added, the mixture was heated from 0 to 90° in 20 min, with swirling. After cooling, the mixture was extracted with ether; the ether solution was dried over anhydrous potassium carbonate and fractionated to give a mixture (6.5 g) of a saturated and an unsaturated ketone.

The mixture was separated into its components by the following method:

The ketone mixture (5.5 g, 0.05 mmole) from the Birch reduction was refluxed with piperidine for 4 hr. The mixture was cooled and poured into 100 ml of 10% (w/v) hydrochloric acid solution. The resulting solution after extraction with ether (30 ml x 5), was made alkaline with 20% sodium hydroxide and again extracted with ether (40 ml x 5). The latter ether extracts were combined, dried over potassium carbonate and fractionated to give 9.0 g of the aminoketone, 3-(1-piperidyl)-6-methylcyclohexanone.

The piperidinoketone obtained as above (0.04 mole) was dissolved in methyl iodide (0.30 mole). The mixture was kept at 5° for 3 hr and the temperature was allowed to rise to 20° over another 3 hr period.

After 12 hr at that temperature, the solid mass was scraped from the flask, pressed onto a filter and dried in air. It crystallised from *n*-butyl alcohol to give crystals of 3-(1-piperidyl)-6-methylcyclohexanone methiodide (8 g), m.p. 172-175°C (reported[2] m.p. 174.5-175°C).

A mixture of 3-(1-piperidyl)-6-methylcyclohexanone methiodide (6.5 g, 0.02 mole) and pyridine (0.06 mole) was heated on a hot water-bath with occasional stirring until solution was complete. The solution was then heated and stirred a further 1 hr at 90° and was then poured, while still warm, into 80 ml of 10% (w/v) hydrochloric acid solution. The mixture was extracted with ether (40 ml x 5), and the ether solution was dried (Na_2SO_4) and fractionated to give 1.5 g of 6-methyl-2-cyclohexen-1-one; ν_{max} ($CHCl_3$): 1680 cm^{-1} (s, unsaturated >C=O group); P.M.R. (δ ppm): 6.92 (1H, dt, $J_{3/2}$ = 10.0 Hz, $J_{3/4a,4b}$ = 3.0 Hz, H-C_3); 5.95 (1H, d, $J_{2/3}$ = 10.0 Hz, H-C_2); 2.95-1.6 (5H, multiplets); 1.45 (3H, d, J = 6.5 Hz, 3H-C_7). Mass Spec.: m/e 110 (M^+, 25), 74 (20), 69 (20), 68 (100%).

The 2,4-dinitrophenylhydrazone derivative had m.p. 159-162° (reported[4] m.p. 161-162°C).

2. Preparation of 3-(2-Nitro-2-propyl)-6-methylcyclohexanone (III)

A mixture of 6-methyl-2-cyclohexen-1-one (1.1 g, 0.01 mole), sodium ethoxide (0.74 g, 0.01 mole) and 2-nitropropane (0.89 g, 0.01 mole) in 75 ml of absolute ethanol was refluxed for 5 hr, cooled and added to ice-water (60 ml). The cooled mixture was acidified with 5% (w/v) hydrochloric acid and extracted with ether (40 ml x 3). The ether solution was dried (Na_2SO_4) and evaporated *in vacuo* to give a heavy oil (1.9 g).

Analytical t.l.c. ($CHCl_3$) showed the presence of one major (higher R_f) and one minor component. The mixture was separated by

chloroform elution on a short column of silica gel G_1. The major component (1.7 g; >90% of the total mixture) was obtained as a heavy oil, ν_{max} ($CHCl_3$): 1710 cm^{-1} (s, >C=O), 1540 cm^{-1} (s, $-NO_2$ group); P.M.R. (δ ppm): 2.4-1.7 (7H, multiplets), 1.58 (6H, s, 2 geminal C-methyl groups); 1.3 (1H, m); 1.0 (3H, d, J = 6.5 Hz). Mass Spec.: m/e 199 ($M^{+\cdot}$, 8), 154 (9), 153 (100), 135 (18), 111 (22), 109 (21), 97 (30), 83 (68).

3. Preparation of ethylene ketal of 3-(2-nitro-2-propyl)-6-methyl-cyclohexanone

A solution of 3-(2-nitro-2-propyl)-6-methylcyclohexanone (III) (1.65 g, 0.0083 mole), ethylene glycol (0.7 g) and *p*-toluenesulphonic acid (110 mg) in 75 ml of anhydrous benzene was refluxed for 20 hr with a Dean and Stark separator to remove water. The solution was cooled to room temperature, washed with 5% sodium bicarbonate solution, dried (Na_2SO_4) and evaporated *in vacuo* to give 1.93 g of a heavy oil which crystallised on freezing. It recrystallised from chloroform in colourless needles, m.p. 67-68°C, ν_{max} ($CHCl_3$): 1540 cm^{-1} (s, $-NO_2$ group); P.M.R. (δ ppm): 3.95 (4H, s, $-O-CH_2-CH_2-O-$); 2.30 (1H, m), 1.8-1.0 (7H, multiplets); 1.52 (6H, s, $>C(CH_3)_2$); 0.85 (3H, d, J = 6.0 Hz). Mass. Spec.: m/e 243 ($M^{+\cdot}$, 5), 213 (7), 197 (15), 155 (100), 113 (80), 99 (40), 69 (70). Analysis: C, 59.02; H, 8.56; N, 5.72; calc. for $C_{12}H_{21}NO_4$: C, 59.22; H, 8.70; N, 5.75%.

4. Preparation of the amino-ketal (IV)

To a 2-necked flask flushed with nitrogen, was added 35 mg of 10% palladium on carbon followed by 10 ml of water. A suspension of 500 mg of sodium borohydride in 10 ml of water was quickly added, and nitrogen

was passed through the solution. The nitro-compound (IIIa) (1.75 g, 0.007 mole) in 20 ml of methanol was added over a period of 5 min. Nitrogen was passed through the solution for another hour. Excess sodium borohydride was reacted with more methanol, then the solution was filtered off and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to give 1.45 g of a heavy oil which crystallised on freezing. The product (higher R_f) was separated from the unreacted nitro-compound (<5% of the total mixture) by short column chromatography (eluted by 10% MeOH/$CHCl_3$) yielding 1.30 g of the amino-ketal (IV) which was recrystallised from chloroform, on chilling, as colourless needles, m.p. 106-107°C, ν_{max} ($CHCl_3$): 3200-3400 cm^{-1} (-NH); P.M.R. (δ ppm): 6.2 (2H, broad, exchangeable with D_2O, $-NH_2$); 3.85 (4H, s, $-O-CH_2-CH_2-O$); 1.9-1.1 (8H, multiplets); 1.02 (6H, s, $>C(CH_3)_2$); 0.85 (3H, d, J = 6.5 Hz). H.R.M.S.: m/e 213 (M^+, 10). Meas.: 213.1718; calc. for $C_{12}H_{23}NO_2$: 213.1729, 198 (25), 156 (100), 155 (99), 139 (20), 113 (41), 99 (29).

5. Preparation of 3-indolyloxalyl chloride

To a stirred solution of indole (3.75 g, 0.03 mole) in 100 ml of anhydrous ether at 0-5°C, oxalyl chloride (4.0 g) was added dropwise during 30 min; stirring and cooling were continued for 1 hr more. The resulting yellow crystals were collected on a filter, washed with anhydrous ether and dried *in vacuo* over KOH to give 5.2 g (78%) of a crude product which was recrystallised from benzene, in yellowish needles, m.p. 134-135°C dec. (lit.[5], m.p. 135° dec.). The amide derivative showed m.p. 255-258°C dec. (lit.[5], m.p. 257-258° dec.).

6. Reaction of 3-indolyloxalyl chloride with the amino-ketal (IV)

To a solution of sodium carbonate (1.6 g) in 40 ml of water at 0° was added 1.1 g (0.005 mole) of the amino-ketal (IV) and 60 ml of dichloromethane. To this vigorously stirred two-phase system was added 1.25 g (0.06 mole) of 3-indolyloxalyl chloride in small portions over a period of 4 min. After the addition had been completed, the stirring was continued for another 50 min. The layers were separated, the aqueous phase was extracted thoroughly with dichloromethane, and the organic fractions were combined. The dichloromethane extracts were washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield 1.8 g of the crude amide.

The crude material was purified by p.t.l.c. (5% MeOH/$CHCl_3$) to give 1.5 g (75%) of the pure amide (V) as an oil, ν_{max} ($CHCl_3$): 3200-3300 cm^{-1} (-NH), 1610-1640 cm^{-1} (s, -C(=O)-C(=O)-NH-); Mass Spec.: m/e 384 (M^+, 2), 279 (5), 229 (6), 196 (9), 155 (30), 149 (35), 144 (80), 139 (70), 113 (100).

7. LAH reduction of (V)

A mixture of the amide (V) (1.4 g, 0.0036 mole), and lithium aluminium hydride (LAH), (1.0 g) in 70 ml of tetrahydrofuran (THF) was refluxed for 5½ hr. The excess lithium aluminium hydride was removed by cautious dropwise addition of water. The solvents were evaporated *in vacuo* and the residue was treated with water (50 ml) containing a few drops of sodium hydroxide solution (10%) and the mixture was extracted with chloroform (30 ml x 4). The chloroform extract was dried (Na_2SO_4) and evaporated *in vacuo* to give 1.25 g of a residue.

Analytical t.l.c. (5% MeOH/$CHCl_3$) showed the presence of

major and minor components. The major component (VI) (lower R_f) was separated by p.t.l.c. (5% MeOH/$CHCl_3$) as an oil (0.8 g, 60%), ν_{max} ($CHCl_3$): 3400 cm^{-1} (-NH), 3200-3350 cm^{-1} (-NH); P.M.R. (δ ppm): 8.2 (1H, broad, exchangeable with D_2O, H-N_a); 7.7-7.05 (4H, multiplets, aromatic protons); 7.02 (1H, d, H-C_2); 3.88 (4H, s, O-CH_2-CH_2-O); 3.02 (4H, multiplet, -CH_2-CH_2-N-); 2.0-1.1 (8H, multiplets); 1.1-1.3 (1H, broad, exchangeable with D_2O, H-N_b); 1.02 (6H, s, C-$(CH_3)_2$); 0.84 (3H, d, J = 6.5 Hz). Mass Spec.: m/e 356 (M^{+}, <1%); 341 (2); 226 (75); 201 (100); 144 (65); 130 (30); 113 (35).

8. Hydrolysis of (VI)

The ethylene ketal (0.6 g, 0.0014 mole) was placed in a flask to which was added 50 ml of 6 N hydrochloric acid and 5 ml of methanol. The solution was warmed up for 20 min in a hot water-bath (80-90°C). The solution was cooled, basified with 10% (w/v) sodium hydroxide solution, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give 0.5 g of a single compound which crystallised from ether, m.p. 119-121°C. The product had identical t.l.c. and spectroscopic data (R_f, u.v., i.r., p.m.r. and m.s.) to natural fruticosonine (II), but was optically inactive.

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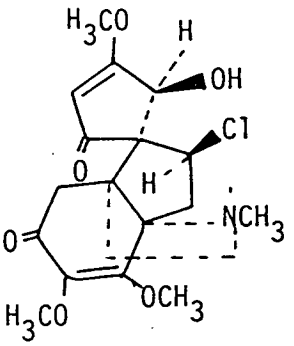
APPENDIX I

I. Introduction

Pachygone, a member of the family *Menispermaceae*, is a small genus of scandent shrubs which are distributed mainly in New Caledonia, North Queensland and the Indo-Malaysian region. Phytochemical investigations on only two species of this genus have been carried out: *Pachygone pubscens*, a species from Northern Queensland, has been shown to contain the bisbenzyl-isoquinoline alkaloid isotrilobine (I) along with the chlorine-containing bases acutumine (II) and acutumidine (III).[1] On the other hand, the Indian species, *Pachygone ovata*, contains N-methylcrotsparine (IV), reticuline (V), liriodenine (VI), trilobine (VII) and coclaurine (VIII).[2]

II. Results and Discussions

Leaves and branches of *Pachygone vieillardii* (5 Kg) were collected in New Caledonia in December, 1976. Extraction by standard methods afforded 3.4 g ($\tilde{\sim}$0.07%) of a crude mixture of alkaloids which were initially separated by a Gallenkamp Craig counter-current apparatus into three fractions. Separation and purification of the individual fractions were carried out by p.t.l.c. Altogether five bases including the known bisbenzyl-isoquinoline alkaloid, daphnoline (IX), were isolated. The remaining four bases have not been completely characterised. A tentative structure is proposed for each of them.



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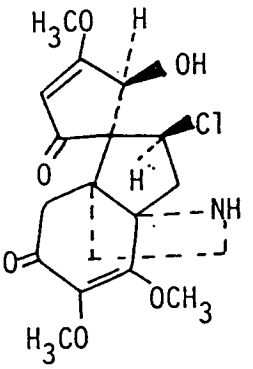

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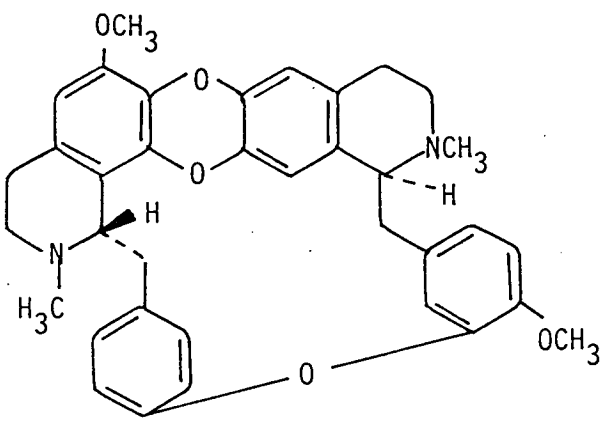

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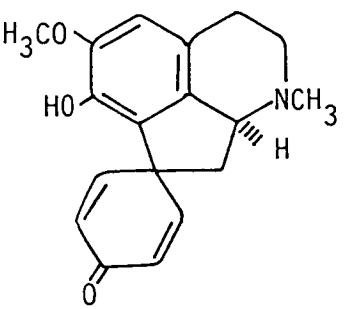

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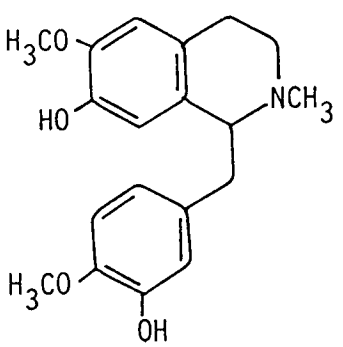

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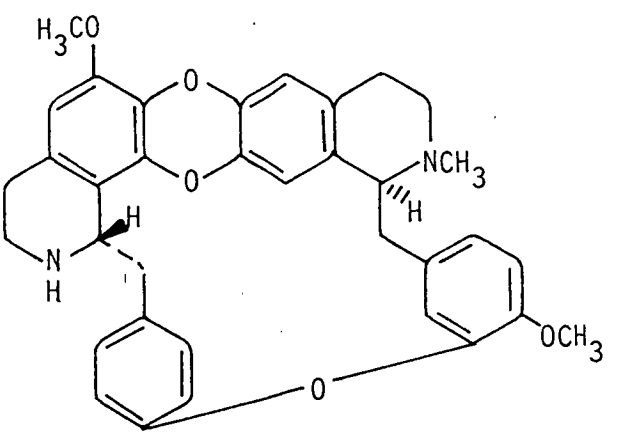

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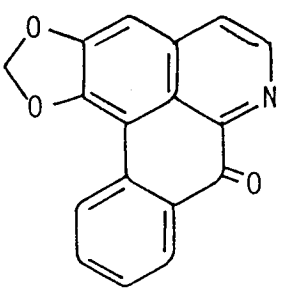

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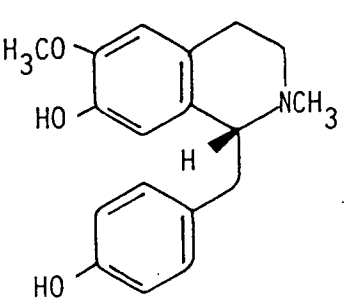
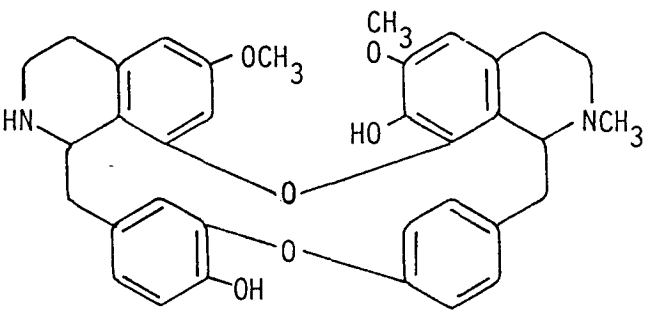


VIII

1. Structure of Daphnoline

Daphnoline was isolated in 0.001% yield from the dry plant material. It crystallised from chloroform in fine colourless needles, m.p. 193-195°C, $[\alpha]_D^{22}$ + 436° ($CHCl_3$). Its P.M.R. spectrum, which was practically identical with that of daphnoline (IX) previously isolated by Bick,[3] showed the presence of ten aromatic protons, two methoxyl groups and one N-methyl group.



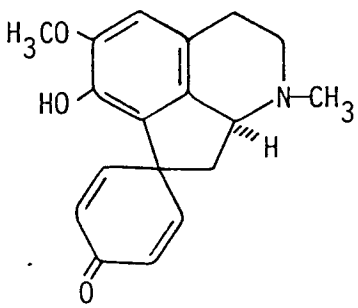
IX

The identity was finally established by a direct comparison of its R_f, [α], m.p., m.m.p., i.r., u.v., p.m.r. and mass spectra with those of an authentic sample previously isolated from *Daphnandra aromatica*.[3]

2. Structure of Alkaloid P_1

P_1 has a molecular formula $C_{18}H_{19}NO_3$ as found by high-resolution mass spectrometry. It crystallised from benzene in colourless needles, m.p. 223-227°C (dec.), $[\alpha]_D^{22}$ - 24° ($CHCl_3$). It develops a blue colour with ferric chloride solution indicating the presence of a phenolic group, which was further supported by a shift to 312 nm

of the u.v. band at 287 nm on addition of alkali. The strong absorption at 1664 cm^{-1} in the infrared spectrum of P_1 shows the presence of an α,β-unsaturated carbonyl group. In fact, there are two sets of AB-type double doublet signals corresponding to two pairs of olefinic protons (αα' and ββ') present in the P.M.R. spectrum of P_1.



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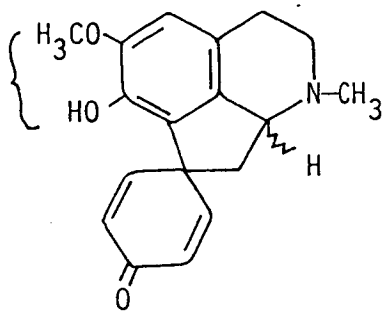
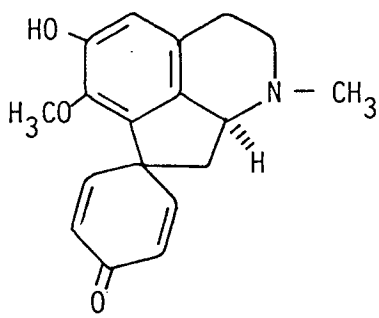
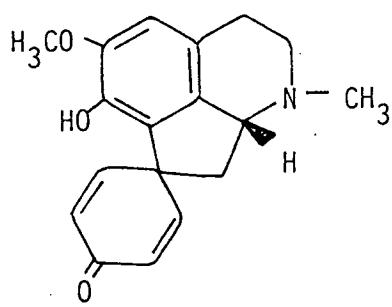


X



XI



XII

The only aromatic proton appears at 6.59 ppm as a singlet. The P.M.R. spectrum also shows signals for one methoxyl group (at 3.82 ppm) and one N-methyl group (at 2.40 ppm). So far, the data point to a partial structure (X) for P_1. The possibility of an -OH group being attached to C-2 can be ruled out from the difference in the ultraviolet absorption patterns of homolinearsine (XI) (with -OH on C-2) and P_1. Thus P_1 is identical to either glaziovine (XII) or

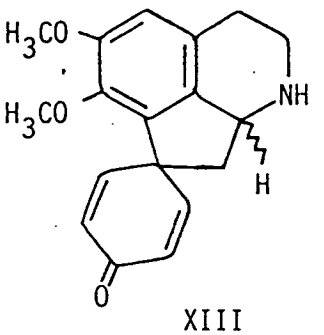
N-methylcrotsparine (IV). However, the methoxyl group signal in glaziovine appears at 3.85 ppm in its P.M.R. spectrum compared to 3.82 ppm in the P.M.R. spectra of both P_1 and N-methylcrotsparine. The signals for N-methyl and the olefinic protons in the last two cases also have the same chemical shifts.* Thus P_1 can be assigned the same structure (IV) as N-methylcrotsparine.[2] Lack of material precluded its complete identification, and its transformation to the corresponding aporphine.

3. Structure of Alkaloid P_2

From its molecular formula $C_{18}H_{19}NO_3$, established by high-resolution mass spectrometry, P_2 is isomeric with P_1. However, P_2 gives a negative $FeCl_3$ test for the presence of a phenolic group and moreover its P.M.R. spectrum as compared to that of P_1 shows the presence of two methoxyl groups instead of one, and the absence of an N-methyl group. The infrared spectra of P_1 and P_2 are very similar and show the presence of an α,β-unsaturated carbonyl group. The P.M.R. spectrum of P_2 also shows signals for two pairs of olefinic protons ($\alpha\alpha'$ and $\beta\beta'$) appearing as two sets of AB-double doublets. There is only one aromatic proton signal at 6.65 ppm in the P.M.R. spectrum of P_2.

This evidence suggests that P_2 possibly has the same skeleton as stepharine (XIII). However owing to insufficient material, a direct comparison with stepharine, or conversion to a known alkaloid has not been possible.

*Moreover, P_1 has a specific rotation of -34° compared to -45.7° for N-methylcrotsparine and +7° for glaziovine, and hence the possibility of a glazivine structure can be excluded.



XIII

4. Structure of Alkaloid P_3

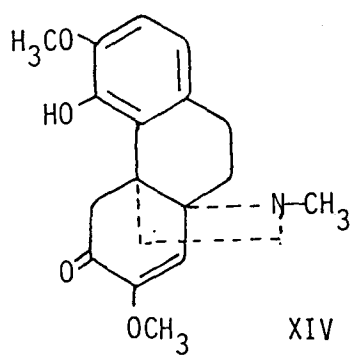
P_3 has been isolated in 0.002% yield. It could not be crystallised, but has $[\alpha]_D^{22}$ - 70° ($CHCl_3$). It has a molecular formula $C_{19}H_{23}NO_4$ as determined by high-resolution mass spectrometry. P_3 gives a positive Gibb's test indicating that it has a phenolic group with its para-position free. The strong infrared band at 1685 cm^{-1} shows the presence of an α,β-unsaturated carbonyl group.

The P.M.R. spectrum of P_3 shows signals for two $-OCH_3$ groups (at 3.92 and 3.66 ppm) and one $N-CH_3$ group (at 2.36 ppm). P_3 also shows signals for two aromatic protons appearing as a AB-double doublet between 6.84 and 6.66 ppm (J = 8.0 Hz). There is only one olefinic proton appearing at 7.74 ppm as a singlet in the P.M.R. spectrum.

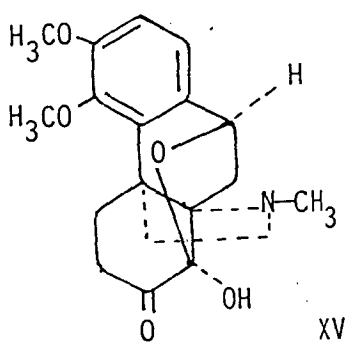
All these data suggest the possibility of either a hasubanan or a morphinane type of skeleton in P_3, with one of the methoxyl groups attached to an olefinic carbon. This inference is supported by the ultraviolet spectrum of P_3 with absorptions at 209, 233 and 264 nm.

However, from a comparison of the mass spectrum of P_3 with those of hasubanan or morphine alkaloids, the presence of the former

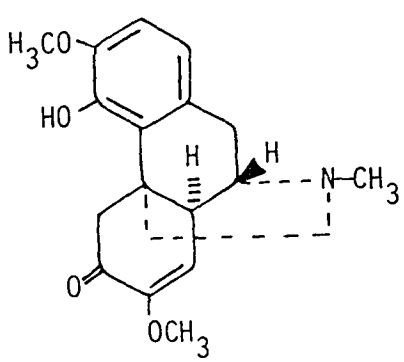
type of skeleton can be excluded, since, in the case of most of the hasubanan alkaloids, the base peak is formed by a fragmentation of the type shown in Scheme 1.[4] In the mass spectrum of metaphanine (XV, M^{+}, 345), the base peak appears at m/e 245. There is a corresponding peak at m/e 231 (of less intensity in the mass spectrum of cepharamine (XIV, M^{+}, 329)). The other important fragments present in the mass spectra of these as well as in the mass spectra of other hasubanan alkaloids appear at m/e 244, 230 and 213, whereas the mass spectra of the morphine alkaloids, e.g. sinomenine (XVI) or isosinomenine (XVII), these fragments are absent, and instead ion peaks, such as 329 (M^{+}), 314 (M-15), 286 (M-43), 192, 178 and 146 appear.[5] The origin of the strong ion peak at m/e 192 in (XVI) and (XVII) is shown in scheme 2.[5] P_3 has also a strong m/e 192 (60%) peak in addition to those at m/e 329, 314 (base peak) and 286 in its mass spectrum; on the other hand, the peaks at m/e 178 and 146 are missing.



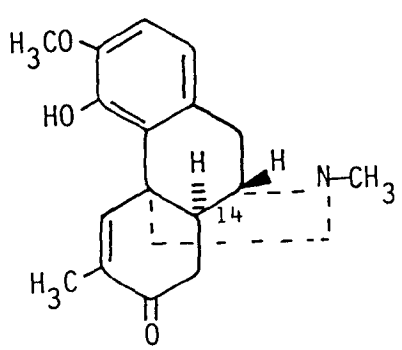
XIV



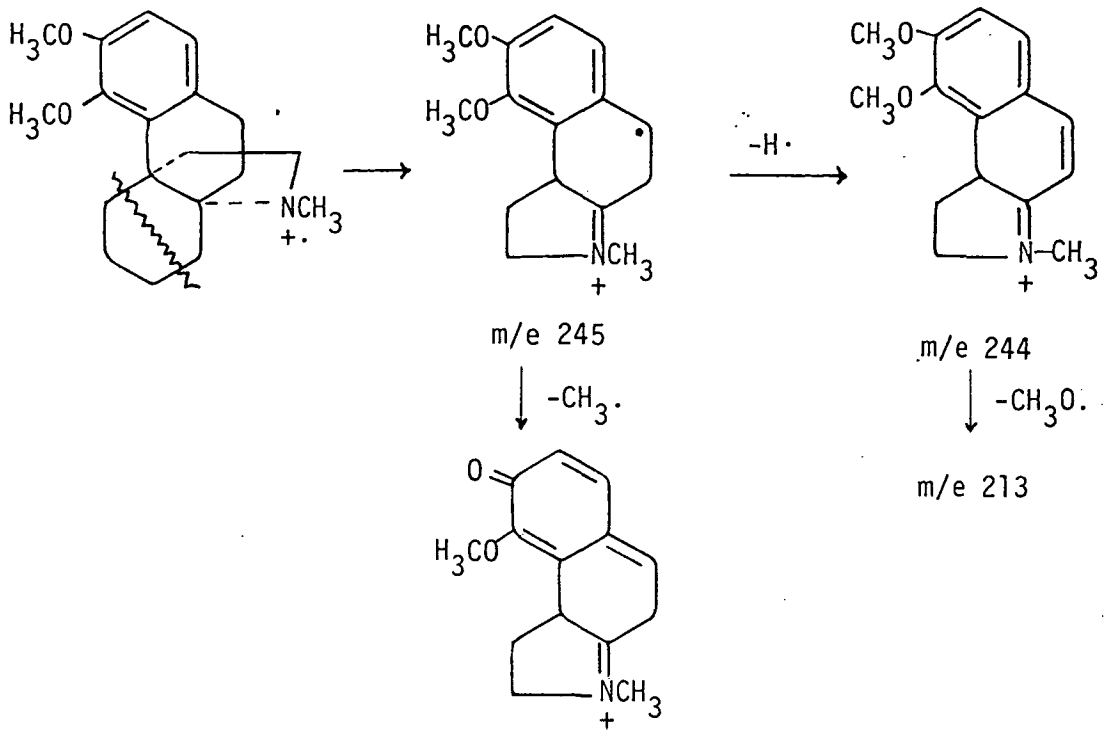
XV



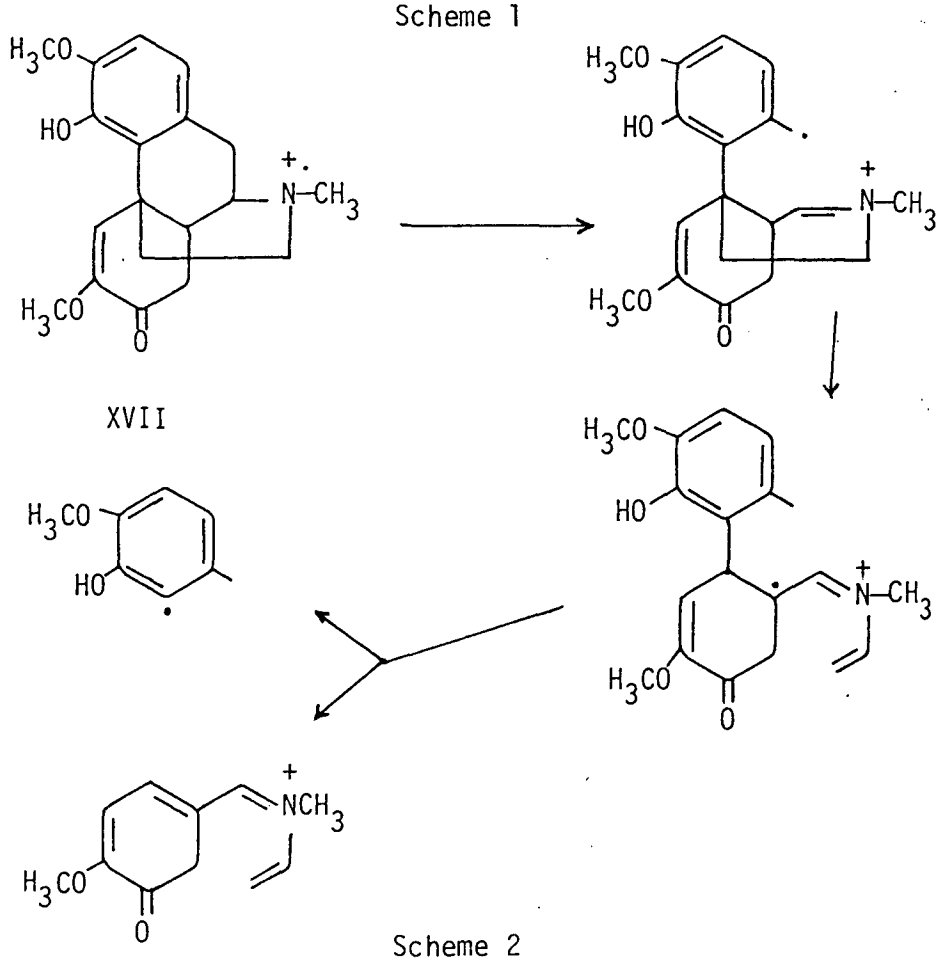
XVI



XVII

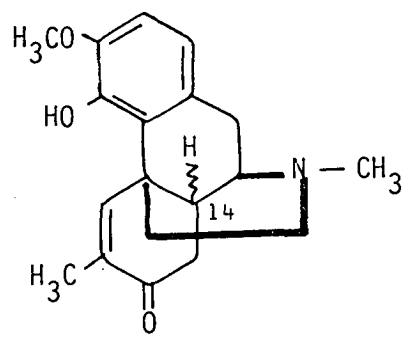


Scheme 1

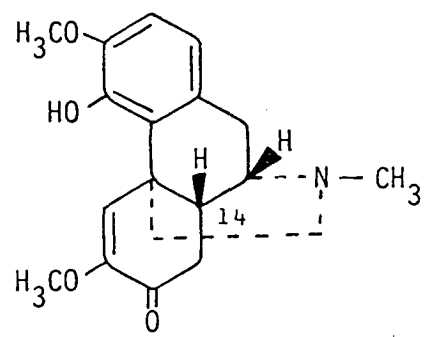


Scheme 2

The ultraviolet and P.M.R. spectra of P_3 are similar to those of 8,14-dihydrosalutaridine (XVIII), sinomenine (XVI) and isosinomenine (XVII). The sinomenine (XVI) and 8,14-dihydrosalutaridine (XVIII) structures can, however, be excluded on the grounds that the olefinic proton signal in the P.M.R. spectrum of P_3 appears far downfield at (7.74 ppm), as compared to 5.47 and 6.76 ppm in the case of (XVI) and (XVIII).



XVIII



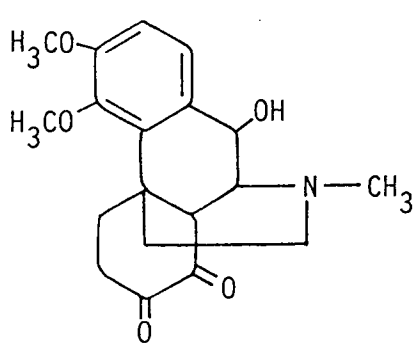
XIX

In the P.M.R. spectrum of isosinomenine also, the olefinic proton is upfield of that in P_3. To account for the low-field resonance (7.74 ppm) of the olefinic proton in P_3, a structure such as (XIX) is suggested. This structure is epimeric with isosinomenine (XVII) at C-14, and the olefinic proton is better deshielded by the aromatic nucleus as compared to isosinomenine (XVII). The alkaloid ocobotrine, isolated from the menispermaceous plant *Ocotea brachybotra* has also been assigned the same structure (XIX)[6] as is suggested for P_3. Their N.M.R. spectra are very similar except that the aromatic proton signals in the case of ocobotrine have been reported to appear as two singlets at 6.75 and 6.73 ppm. The C-5 olefinic proton signal appears at 7.76 ppm in the P.M.R. spectrum of ocobotrine. Both P_3 and ocobotrine have similar mass spectral fragmentation patterns.

Insufficient material precluded a direct comparison with ocobotrine.

5. Structure of Alkaloid P_4

P_4 has a molecular formula $C_{19}H_{23}NO_5$ as established by high-resolution mass spectrometry, and a specific rotation of $[\alpha]_D^{22}$ + 121° ($CHCl_3$). P_4 gives a negative $FeCl_3$ test and a negative Gibb's test indicating the absence of a phenolic group. The P.M.R. spectrum of P_4 shows signals for two $-OCH_3$ groups (at 3.87 and 3.71 ppm) and one $N-CH_3$ group (at 2.33 ppm). The P.M.R. spectrum also has signals for two aromatic protons appearing as a AB-double doublet between 7.0 and 6.78 ppm (J = 8.0 Hz). The strong infrared bands at 1764 cm^{-1} and 1730 cm^{-1} suggest the possibility of a 1,2-diketone system in the molecule. This inference is further supported by a strong M-43 (m/e 302) peak in the mass spectrum of P_4. The loss of 43 mass units, which is equivalent to a loss of C_2H_3O, could be due to the loss of a methyl group followed by a molecule of CO from the diketone system. The fifth oxygen atom is present as an alcoholic group, as shown by the presence of a band at 3500 cm^{-1} in the infrared spectrum.



XX

The presence of two ortho-aromatic protons and two methoxyl groups, along with the absence of olefinic protons, suggests that P_4 has either a hasubanan or morphinane type of skeleton. The presence of the former type of skeleton can be excluded on the grounds that the mass spectrum of P_4 does not contain any peak at m/e 245, 244, 230 or 213; a morphinane type of structure such as (XX) is thus indicated for P_4. However, owing to insufficient material, a complete structural elucidation has not been possible.

Experimental

1. Extraction procedure

Leaves and branches of *Pachygone vieillardii* collected in New Caledonia were air-dried and ground to a fine powder (5.0 Kg) in a Wiley mill. The dry powder was exhaustively extracted with methanol at room temperature until a test sample gave a negative test with Mayer's reagent. The extract was concentrated *in vacuo* at a temperature below 40°C, to a thick brown syrup, which was dissolved in 750 ml of warm glacial acetic acid. The resulting solution was poured into 20 ℓ of water whilst rapidly agitating the solution with a vibromixer. The solution was left to stand overnight, and the precipitate that settled out was filtered off, washed with very dilute acid until free from alkaloids, and then discarded. The washings were combined with the original filtrate and evaporated *in vacuo* at a temperature below 35°C to dryness. The residue was treated with 2 ℓ of water and evaporated again to dryness. The process of dilution with water and evaporation to dryness was repeated once more to get rid of most of the acetic acid. Finally, the residue was treated with 2 ℓ of water and the mixture was basified

with ammonia (d, 0.88). The resulting mixture was extracted with chloroform (200 ml x 6). The combined chloroform extracts were washed with water, dried (Na_2SO_4) and finally evaporated to dryness *in vacuo* to give 3.4 g ($\sim$0.070%)of crude alkaloids.

2. Initial separation procedure

The crude alkaloid mixture (3.4 g) was dissolved in chloroform (40 ml) and introduced into the first tube of a Gallenkamp Craig counter-current apparatus coupled to an automatic fraction collector. The machine was programmed to shake for 2½ min after each settling interval of 20 min. The crude alkaloids were subjected to counter-current distribution using chloroform as the stationary phase and 1×10^{-3} N sulphuric acid as the mobile phase. About 40 ml of mobile phase was transferred at the end of each interval, and every tenth transfer was monitored by analytical t.l.c. (12% MeOH/$CHCl_3$) after basification and extraction of an aliquot of the aqueous eluent with chloroform. The fractions were bulked accordingly and the bulking summary is shown in Table I.

Table I

Bulking Summary of fractions isolated after counter-current distribution

Tube Nos.	Fraction	Wt. of recovered alkaloids (g)
15-59	1	1.00
60-109	2	0.80
110-175	3	0.39
Craig machine left-over		gave a faint positive test with Mayer's reagent.

3. Isolation, purification and characterisation of the alkaloids

Fraction 1

Analytical t.l.c. (8% MeOH/$CHCl_3$) showed the presence of at least three components. The mixture was separated by p.t.l.c. [(i) 8% MeOH/$CHCl_3$, (ii) 5% $Et_3N/CHCl_3$)] into four bands. The highest R_f band was extracted to give 30 mg of an alkaloid, P_1, which crystallised from benzene in colourless needles, m.p. 223-227°C (dec.), $[\alpha]_D^{22}$ - 34° (C, 0.30, $CHCl_3$); λ_{max} (MeOH): 287 nm (3.47) [312 nm (3.24) in MeOH + KOH], 233 nm (4.38), 213 nm (4.39); ν_{max} ($CHCl_3$): 1664 cm^{-1} (s), 1619 cm^{-1} (m); P.M.R. (δ ppm): 7.08-6.79 (2H, multiplets, α,α'-olefinic protons); 6.45-6.24 (2H, multiplets, β,β'-olefinic protons); 6.59 (1H, s, aromatic proton), 3.82 (3H, s, $-OCH_3$), 3.79-3.38 (2H, multiplets); 3.2-3.0 (1H, m); 2.95-2.8 (2H, multiplets), 2.7-2.55 (1H, m); 2.5-2.2 (1H, m); 2.40 (3H, s, $N-CH_3$). H.R.M.S.: m/e 297 ($M^{+\cdot}$, 100). Meas.: 297.1348; calc. for $C_{18}H_{19}NO_3$: 297.1365, 269 (36), 268 (60), 254 (38), 253 (21), 252 (19), 239 (15), 226 (21), 225 (19), 211 (34), 207 (26), 196 (21), 168 (29), 165 (50), 149 (52), 142 (43), 129 (52), 115 (85). It gave a positive $FeCl_3$ test for phenol.

Extraction of the second (from top) R_f band afforded 16 mg of another alkaloid P_2, which could not be crystallised. It decomposed very readily. P_2 had ν_{max} ($CHCl_3$): 3430 cm^{-1}, 1665 cm^{-1} (s), 1620 cm^{-1} (m); P.M.R. (δ ppm): 7.1-6.8 (2H, multiplets, α,α'-olefinic protons); 6.45-6.27 (2H, multiplets, β,β'-olefinic protons), 6.65 (1H, s, aromatic proton), 3.81 and 3.60 (3H x 2, 2s, 2 $-OCH_3$); Mass Spec.: m/e 297 ($M^{+\cdot}$, 34), 296 (15), 268 (27), 167 (30), 149 (100), 126 (22), 118 (22), 115 (23), 104 (21).

P_2 gave a negative $FeCl_3$ test for phenol.

The third R_f band was extracted to give 45 mg of daphnoline, which

crystallised from chloroform as colourless fine needles, m.p. 193-195°C, $[\alpha]_D^{19}$ + 436° ($CHCl_3$); λ_{max} (MeOH): 286 nm (3.71), 262 nm (3.55); ν_{max} ($CHCl_3$): 3400-3250 cm^{-1} (broad); P.M.R. ($CDCl_3$ + CD_3OD, δ ppm): 7.50-7.35 (1H, m, aromatic proton), 7.05-6.6 (5H, multiplets, aromatic protons); 6.45-6.4 (3H, multiplets, aromatic protons); 5.65-5.5 (1H, m, aromatic proton); 3.82 and 3.6 (3H x 2, 2s, 2 $-OCH_3$); 2.58 (3H, s, $N-CH_3$).

The identity was established by a direct comparison of its [α], R_f, m.p., m.m.p., i.r., u.v., p.m.r. and mass spectra with those of authentic daphnoline.[3]

Further purification of the lowest band extract (300 mg) was not attempted.

Fraction 2

Analytical t.l.c. (12% MeOH/$CHCl_3$) showed the presence of two major alkaloids together with at least two minor components. The mixture was separated by p.t.l.c. [(i) 10% $Et_2NH/CHCl_3$, (ii) 12% MeOH/$CHCl_3$] into three bands. The highest R_f band corresponding to one of the major components was extracted to give an alkaloid P_3 (40 mg) which could not be crystallised from any solvent, but had $[\alpha]_D^{22}$ - 70° (C, 0.39, $CHCl_3$), λ_{max} (MeOH): 264 nm (3.47), 233 nm (3.38), 209 nm (3.94); ν_{max} (KBr): 3500 cm^{-1}, 3350 cm^{-1}, 1685 cm^{-1} 1610 cm^{-1}; P.M.R. (δ ppm): 7.74 (1H, s); 6.84-6.66 (2H, AB-double doublets, J = 8 Hz, aromatic protons); 3.92 and 3.66 (3H x 2, 2s, 2 $-OCH_3$); 3.7-3.4 (1H, m); 3.3-3.0 (2H, multiplets), 2.9-2.8 (2H, multiplets), 2.7-2.4 (3H, multiplets); 2.36 (3H, s, $N-CH_3$); 2.0 (2H, s); 1.26 (1H, br. s, exchangeable with D_2O). H.R.M.S.: m/e 329 ($M^{+\cdot}$, 50). Meas.: 329.1613, calc. for $C_{19}H_{23}NO_4$: 329.1627, 314 (100), 286 (28), 271 (8), 226 (8), 218 (10), 211 (10), 201 (10),

192 (60), 189 (24), 165 (15), 157 (15), 149 (38), 129 (45), 121 (15), 118 (15), 115 (28), 91 (20), 90 (20), 87 (45), 86 (30).

P_3 gave a positive Gibb's test for a phenol with a free para position.

Extraction of the middle band gave 40 mg of an alkaloid which proved to be identical with P_1.

Further purification of the lowest band extract (200 mg) was not attempted.

Fraction 3

Analytical t.l.c. (8% MeOH/$CHCl_3$) showed the presence of one major and at least two minor components. The mixture was separated by p.t.l.c. (8% MeOH/$CHCl_3$) into two bands. The higher R_f band was extracted to give 52 mg of an alkaloid P_4 which gave a negative Gibb's test for phenol. P_4 could not be induced to crystallise, but had $[\alpha]_D^{22}$ + 121° (C, 0.35, $CHCl_3$); λ_{max} (MeOH): 287 nm (3.3), 209 nm (4.22); ν_{max} ($CHCl_3$): 3500 cm^{-1} (m); 1764 cm^{-1} (s), 1730 cm^{-1} (s), 1615 cm^{-1} (m); P.M.R. (δ ppm): 7.0-6.78 (2H, AB-double doublet J = 8.0 Hz, aromatic protons); 3.87 and 3.71 (3H x 2, 2s, 2 O-CH_3); 3.3-2.3 (7H, multiplets); 2.33 (3H, s, N-CH_3); 2.3-1.2 (5H, multiplets). H.R.M.S.: m/e 345 (M^+, 100). Meas.: 345.1566; calc. for $C_{19}H_{23}NO_5$: 345.1593; 344 (39), 314 (18, $C_{18}H_{20}NO_4$); 303 (26, $C_{17}H_{21}NO_4$); 302 (83, $C_{17}H_{20}NO_4$); 300 (17, $C_{18}H_{22}NO_3$); 286 (41, $C_{17}H_{20}NO_3$); 115 (11, C_9H_7); 85 (13).

The extract from the lower band (85 mg) was not further purified.

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APPENDIX II

Synthesis and *X*-Ray Crystal Structure of Fruticosonine, a Novel Indole Alkaloid from a New Zealand *Aristotelia* sp. (Elaeocarpaceae)

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Reprinted from

Journal of The Chemical Society
Chemical Communications
1979

The Chemical Society, Burlington House, London W1V 0BN

Synthesis and *X*-Ray Crystal Structure of Fruticosonine, a Novel Indole Alkaloid from a New Zealand *Aristotelia* sp. (Elaeocarpaceae)

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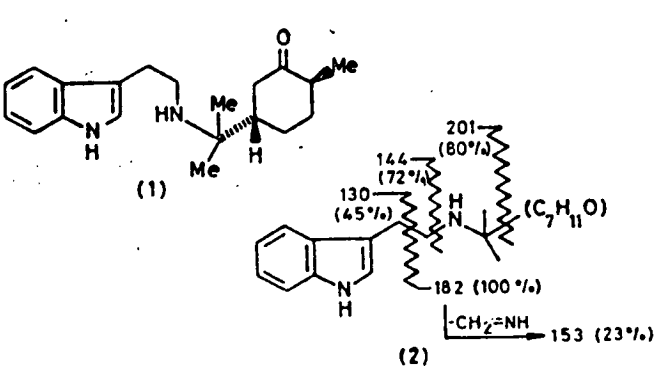
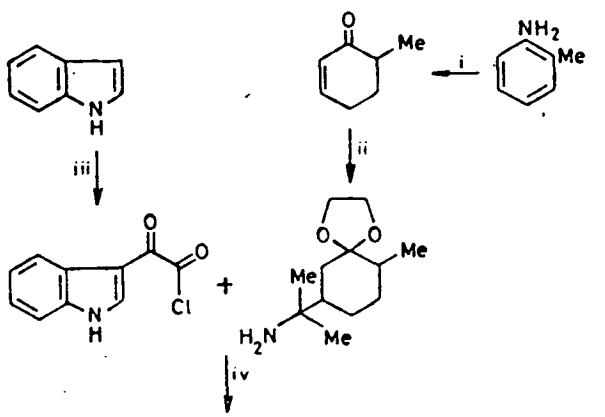
Summary The structure of fruticosonine, a new type of indole alkaloid from *A. fruticosa*, has been determined by *X*-ray crystallography and by synthesis.

A RANGE of novel indole alkaloids has been isolated from *Aristotelia* spp. from Tasmania,[1] New Zealand,[2] and Chile.[3] Another New Zealand species not previously examined, *A. fruticosa* Hook. f., contains small amounts of at least four alkaloids in its roots and stems. One of these, isolated in 0·005% yield from dry plant material, crystallised from ether, m.p. 120—121 °C, $[\alpha]_D^{20}$ + 45·7° (*c* = 0·5, $CHCl_3$). Spectroscopic examination showed it had the molecular formula $C_{20}H_{28}N_2O$ with an open-chain or 6-membered ring oxo group; it also had an indole nucleus unsubstituted at position 2, which was confirmed by a positive Ehrlich test. Furthermore, n.m.r. spectroscopy indicated that two geminal *C*-methyl groups were present, but no olefinic group. The mass spectrum suggested the partial structure (**2**); the presence of two methylene groups between the indole ring and the aliphatic nitrogen atom were in accordance with a 4-proton multiplet between δ 2·96 and 2·86 in the ^1H n.m.r. spectrum, which suggested, moreover, that the $C_7H_{11}O$ fragment could be present as a 2-methylcyclohexanone residue. These tentative deductions have been confirmed by *X*-ray crystallography and by synthesis.



Crystal data: fruticosonine (1), $C_{20}H_{28}N_2O$, M 312·5, tetragonal, $a = 8{\cdot}847(2)$, $c = 47{\cdot}857(9)$ Å; $D_m = 1{\cdot}12(2)$, $D_c = 1{\cdot}108$ g cm^{-3}, $Z = 8$, space group $P4_32_12$, $F(000) = 1360$. Single crystal X-ray data between the limits $6° < 2\theta < 120°$ were measured with a Philips PW 1100 diffractometer, using the ω-scan technique with graphite monochromated Cu-K_α radiation; 1428 unique data [$I \geq 3\sigma(I)$] were recorded. The structure was partially solved using direct methods (MULTAN[4]), and the remaining non-hydrogen atoms were located in the subsequent difference Fourier synthesis. Hydrogen atom co-ordinates were calculated (Sheldrick[5]) and all atomic parameters (non-hydrogen with anisotropic, hydrogen with isotropic thermal parameters) were refined by least-squares techniques. At convergence the R-factor for the 1428 data was 0·062. It was not possible to determine the absolute configuration; structure (1) represents the relative stereochemistry.†



(±)-Fruticosonine (1)

SCHEME. i, Li, NH_3, BuOH (G. Stork and W. N. White, *J. Amer. Chem. Soc.*, 1956, **78**, 4604); ii, (a) Me_2CHNO_2, EtONa, (b) $HOCH_2CH_2OH$, MeC_6H_4-*p*-SO_3H, (c) $NaBH_4$, Pd–C, MeOH; iii, ClCOCOCl (K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, 1958, **23**, 1171); (a) $LiAlH_4$, (b) H_2O, H^+.

Racemic fruticosonine, synthesised by the route shown in the Scheme, had identical spectra to those of the natural base.

Fruticosonine or a close analogue, formed from tryptophan and a simple unarranged terpene unit, probably constitutes an early stage in the biosynthesis of other *Aristotelia* alkaloids.

We thank the Australian Research Grants Committee for support, the Australian Development Assistance Bureau for a Colombo Plan Award (to N. C.) and an Australian Commonwealth Scholarship (to M. A. H.), the C.S.I.R.O. Division of Entomology, Canberra, for high-resolution mass spectra, and the New Zealand Forestry Service for collection of plant material.

(*Received*, 12*th June* 1979; *Com.* 618.)

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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Tetrahedron Letters Vol. 21, pp 545 - 546 0040-4039/80/0201-0545$02.00/0

ARISTOTELINONE AND SERRATOLINE: NEW INDOLE ALKALOIDS FROM *ARISTOTELIA SERRATA* W.R.B. OLIVER

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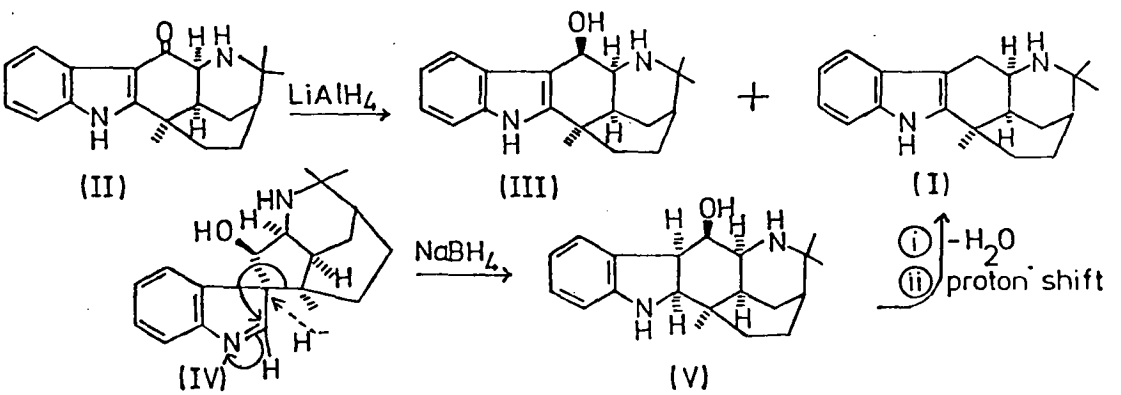
Summary: Aristotelinone and serratoline, two new *Aristotelia* alkaloids, are shown to have indole and indolenine structures respectively from their spectra and reduction products.

The structure and absolute configuration of aristoteline (I), the main alkaloid of the New Zealand plant *A. serrata* (and of the South American *A. chilensis*[2]) was established by X-ray crystallography[1]. A minor alkaloid of *A. serrata*, aristotelinone, was isolated by standard means and crystallised from methanol in fine needles, changing around 255° into longer needles which remained unaltered up to 320°, $[\alpha]_D^{19}$ + 122.7° (MeOH + $CHCl_3$ 1:1). From its molecular formula $C_{20}H_{24}N_2O$, aristotelinone had two less hydrogen atoms than (I), plus an oxygen; its ^{13}C nmr spectrum was largely similar to that of aristoteline, except for a signal due to a carbonyl group, which from the ir and uv spectra was attached to the 3-position of an indole nucleus[3]. This deduction was in accord with the absence of allylic proton signals in the ^1H nmr spectrum, which otherwise resembled that of (I); in both spectra the 2 and 3 positions of indole appeared to be substituted, and this was confirmed by a -ve Ehrlich test.

On LAH reduction of aristotelinone, the crystalline major product proved identical with (I): the structure and stereochemistry of aristotelinone are thus established as (II). Two minor reduction products were evidently the corresponding epimeric secondary alcohols from their spectra and molecular formulae. One of them crystallised, and showed signals in its ^1H nmr spectrum due to protons adjacent to the hydroxyl (δ 3.70), and to the aliphatic nitrogen (δ 2.50), which were weakly coupled (J = 3.1 Hz), and since the latter proton must be axial as in aristoteline (I), the hydroxyl group is also axial as in (III).

Another minor alkaloid from *A. serrata* crystallised as rhombs from methanol, mp 157-160°, with $[\alpha]_D^{19}$ - 68.25° ($CHCl_3$). This base, serratoline, was isomeric with the dihydro-reduction products of aristotelinone, and like them gave a -ve Ehrlich test and had an hydroxyl group from its ir and ^1H nmr spectra. The ms of all three bases were very similar, and the ^1H nmr spectra

of serratoline and (III) showed a particular resemblance: the aliphatic regions were virtually identical, with only slight differences in chemical shifts and coupling constants of certain signals. There were also close similarities in the aromatic region, but the spectrum of (III) had a broad signal at δ 7.88 due to the proton on the indolic nitrogen; this was absent in the serratoline spectrum, which had instead an extra singlet at δ 7.30. The uv spectra of the two bases, however, were different: that of serratoline showed it was an indolenine (λ_{max} 262 nm). Structure (IV) suggested by these data was consistent with the reactions of serratoline, which was unaffected by heating with alkali, and did not rearrange to an indoxyl as would be expected if it had a 3-hydroxy group; on the other hand, it was smoothly reduced by borohydride to a single product with the uv spectrum of an indoline, which on acid-catalysed dehydration readily gave (I). The stereochemistry around the spiro carbon of (IV) is uncertain, but it is probable that on reduction, hydride addition takes place from the less hindered under side, leading to (V) which could readily dehydrate and rearrange to (I).



We are grateful for financial support from the Australian Research Grants Committee, and for an Australian Commonwealth Scholarship (to M.A.H.). We also thank the CSIRO Division of Entomology, Canberra, for high-resolution ms, the National NMR Centre, Canberra, for ^{13}C nmr spectra, and the New Zealand Forestry Service for plant material.

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(Received in UK 5 December 1979)

Separatum
HELVETICA CHIMICA ACTA
Vol. 63, Fasc. 7, p. 2130–2134 (1980)

223. Aristoserratin, ein neues Indolalkaloid aus *Aristotelia serrata* W. R. B. OLIVER und *A. peduncularis* (LABILL.) HOOK. F.

178. Mitteilung über organische Naturstoffe[1][2])

von **Mohammad A. Hai**[a]), **Nigel W. Preston**[a]), **Rolf Kyburz**[b]), **Emanuel Schöpp**[b]), **I. Ralph C. Bick**[a]) und **Manfred Hesse**[b])

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(10.VII.80)

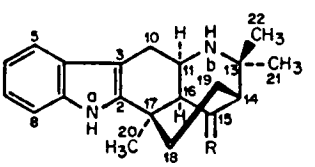
Aristoserratine, a New Indole Alkaloid from *Aristotelia serrata* W. R. B. OLIVER and from *A. peduncularis* (LABILL.) HOOK. F.

Summary

The new indole alkaloid aristoserratine (**2**) has been isolated from *Aristotelia*. Its structure and absolute configuration were elucidated on the basis of spectroscopic data.

Aus *Aristotelia*-Arten (Pflanzenfamilie *Elaeocarpaceae*) wurden in letzter Zeit eine Reihe von Indolalkaloiden isoliert, die sich biogenetisch vermutlich von Tryptamin (= 2-(3-Indolyl)äthylamin) und einem cyclischen Monoterpen ableiten. Aus *A. serrata* wurden bisher die Alkaloide Aristotelin (**1**)[3]) als Hauptbase [2], Aristotelinon [3] und Serratolin [3] isoliert und in ihrer Struktur aufgeklärt. Die entsprechenden Alkaloide aus *A. peduncularis* sind die Hauptbase Peduncularin [4], Sorellin [5], Hobartin [5] und Aristotelin [6].

In der vorliegenden Mitteilung wird über die Strukturaufklärung einer weiteren Base, des Aristoserratins (**2**)[3]), die in kleiner Menge in beiden erwähnten Pflanzen vorkommt, berichtet. Aristoserratin (**2**, $C_{20}H_{24}N_2O$, $M = 308$; $[\alpha]_D = +22{,}5°$) besitzt einen 2,3-disubstituierten Indolchromophor (UV.-, ^{1}H-NMR.-, ^{13}C-NMR.-Evidenz).

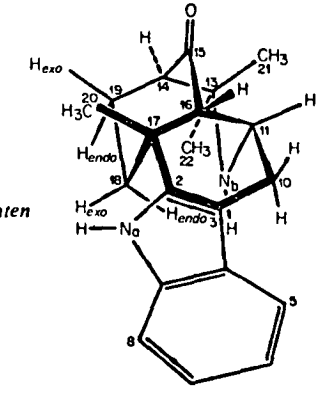


1 R = H_2, Aristotelin[3])
2 R = O, Aristoserratin[3])
3 R = H,OH

[1]) 177. Mitt. s. [1].
[2]) Teil der geplanten Dissertation von *R. K.*, Universität Zürich.
[3]) Für die *Aristotelia*-Alkaloide wird entsprechend den biogenetischen Vorstellungen die in **1** und **2** angegebene Atom-Numerierung vorgeschlagen, vgl. [6]. Der systematische Name von **1** lautet: 2,2,5-Trimethyl-3,5-äthano-1,2,3,4,4a,5,11,11a-octahydropyrido[2,3-*b*]carbazol.

0018-019X/80/7/2130-05$01.00/0

Tabelle. *Gemessene chemische Verschiebungen (in ppm) und Kopplungskonstanten (in Hz) aliphatischer Protonen im NMR.-Spektrum von Aristoserratin* (**2**)



Protonen	Hexo–C(10)	Hendo–C(10)	H–C(11)	H–C(16)	H–C(14)	Hexo–C(19)	Hendo–C(19)	Hexo–C(18)	Hendo–C(18)	Chem. Verschiebungen
Hexo–C(10)		16,8	5,7[a])							3,08
Hendo–C(10)	16,8		1,5[a])							2,80
H–C(11)	5,7[a])	1,5[a])		2,5[a])						3,79
H–C(16)			2,5[a])		1,3[a])					2,35
H–C(14)				1,3[a])		3,8	2,5			2,08
Hexo–C(19)					3,8		14,2	5,6[a])	13,8[a])	1,92
Hendo–C(19)					2,5	14,2		2,0[a])	5,8[a])	2,18
Hexo–C(18)						5,6[a])	2,0[a])		13,8[a])	1,65
Hendo–C(18)						13,8[a])	5,8[a])	13,8[a])		2,58

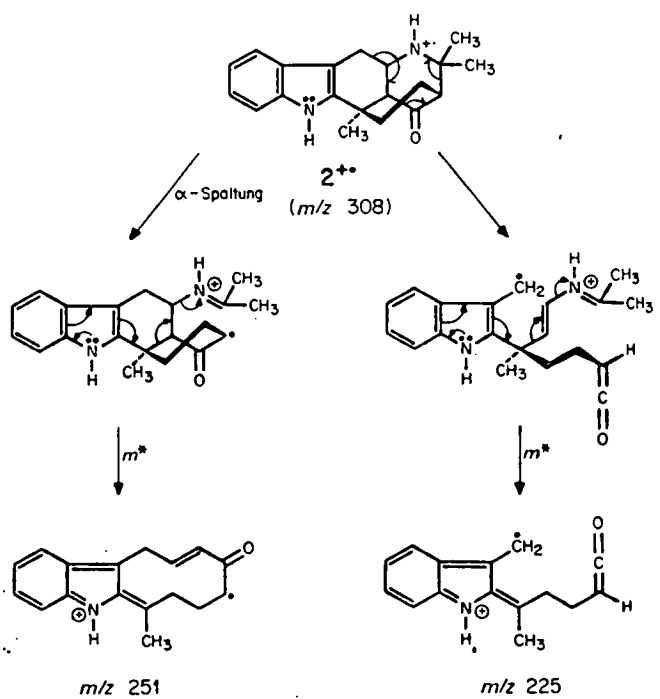
[a]) Entkopplungsexperiment, vgl. exper. Teil.

Das IR.-Spektrum ($CHCl_3$) enthält zwei NH-(3473, 3330 cm^{-1}) und eine Keton-(1710 cm^{-1})Bande. Im ^1H-NMR.-Spektrum werden zwei ungekoppelte Signale von drei Methylgruppen bei 1,38 (3 H) und 1,19 ppm (6 H) registriert. Bei 8,18 (*s*) und *ca.* 1,5 ppm (*s*) erscheint je ein HN-Signal. Die Resonanzlinien der Protonen am aromatischen Ring liegen zwischen 7,47 und 7,09 ppm, vgl. exper. Teil. Aus der *Tabelle* sind die chemischen Verschiebungen und das Kopplungsmuster der restlichen, am aliphatischen Teil haftenden Protonen aufgeführt.

Das ^{13}C-NMR.-Spektrum von **2** enthält im Bereich der sp^3-Kohlenstoffatome (57,4 und 39,7 ppm) zwei Signale von quaternären Zentren, welche die drei Methylgruppen tragen. Die Verschiebung des Signals bei tiefem Feld deutet auf die Verknüpfung mit dem N_b-Atom hin, das andere quaternäre Zentrum muss am Indolteil gebunden sein, da weitere allylische Signale fehlen. Diese Befunde stehen im Einklang mit dem Massenspektrum: N_b ist einerseits an C(11) gebunden (chemische Verschiebung von H–C(11)), anderseits an ein quaternäres Kohlenstoffatom ($\delta = 57{,}4$ ppm), welches zwei Methylgruppen trägt (Fragment-Ion *m/z* 251 im Massenspektrum, vgl. *Schema*). Im übrigen stehen das ^{13}C-NMR.- und das Massenspektrum in Übereinstimmung mit der postulierten Struktur **2**.

Der Basispik im Massenspektrum von **2** ist *m/z* 225 ($C_{15}H_{15}NO$). Ein entsprechendes Ion wird auch in den Spektren von Aristotelin (**1**) bei *m/z* 211 und dem $NaBH_4$-Reduktionsprodukt **3** von **2** bei *m/z* 227 registriert. Im Vergleich zu den jeweiligen Molekular-ionen ist *m/z* 225 doppelt so intensiv wie *m/z* 211 und 227. Dies

Schema. *Die Ionen m/z 251 und 225 im Massenspektrum von Aristoserratin* (**2**)



bestätigt den vorgeschlagenen Fragmentierungsmechanismus, der den Bruch der in 2^+ stärker aktivierten C(13)–C(14)-Bindung begünstigt.

Mit den bisher diskutierten spektroskopischen Daten sind die Bindungen C(16)–C(17), C(17)–C(18) und C(13)–C(14) nicht direkt bewiesen. Die Existenz der C(13)–C(14)-Bindung allerdings ist aufgrund massenspektrometrischer Argumente sehr wahrscheinlich gemacht. Ausserdem stehen H*endo*–C(18) und H*exo*–C(19) *trans*-diaxial ($^3J_{H,H} = 13{,}8$ Hz, vgl. *Tab.*); diese sterische Bedingung wird unter allen jetzt noch denkbaren Strukturen einzig im angegebenen Vorschlag **2** erfüllt. Aus biogenetischen Erwägungen - Annahme von Tryptamin als Vorläufer - wird eine umgekehrte Reihenfolge der Substituenten an C(2) und C(3) ausgeschlossen.

Aufgrund der folgenden Argumente repräsentiert **2** die absolute Konfiguration von Aristoserratin. Eine direkte Korrelation von **2** mit dem in seiner absoluten Konfiguration bekannten Aristotelin (**1**) [2] war bisher nicht möglich. Das Keton **2** zeigt im CD.-Spektrum (Äthanol) bei 302 nm einen positiven *Cotton*-Effekt ($n \rightarrow \pi^*$-Übergang der Carbonylgruppe), was aufgrund der Oktantenregel mit **2** in Übereinstimmung steht. Ferner enthält das CD.-Spektrum von **2** noch zwei negative *Cotton*-Effekte bei 227 und 278 nm, welche vom Indolchromophor verursacht werden. Im CD.-Spektrum von **1** wird nur der kurzwelligere beobachtet. Da in **1** und **2** dieser Effekt das gleiche Vorzeichen hat, kann auch in diesem Fall auf die gleiche absolute Konfiguration geschlossen werden [7].

Wir danken dem *Australian Research Grant Committee* und dem *Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung* für finanzielle Unterstützung, dem *Australian Development Assistance Bureau* für ein *Australian Commonwealth Scholarship (M.A.H.)*. Ferner sind wir dem *New Zealand Forestry Service* für das Sammeln von Pflanzenmaterial, den Herren Dr. *R. Hollenstein* und Dipl.-Chem. *T. Jenny* für NMR.-Spektren und *N. Bild* (alle Universität Zürich) für Massenspektren dankbar.

Experimenteller Teil

1. *Allgemeine Bemerkungen.* Vgl. [5]. CD.-Spektren wurden auf einem *Roussel-Jouan*-Dichrographen, Modell 185, gemessen, Angaben in nm ($\Delta\varepsilon$). - NMR.-Spektren in $CDCl_3$ auf *Varian* EM 390 (^{1}H-NMR. bei 90 MHz), *Varian* XL 100 (^{13}C-NMR. bei 25,2 MHz), *Varian* XL 200 (^{1}H-NMR. bei 200 MHz) und auf einem 270-MHz-Spektrometer von *Bruker* (^{1}H-NMR. bei 270 MHz).

2. *Isolierung und Reinigung von* **2**. Vgl. [5]. Gefundene Alkaloidgehalte (bezogen auf die trockene Droge): 0,0025% in *Aristotelia serrata* W.R.B. OLIVER und 0,00015% in *Aristotelia peduncularis* (LABILL.) HOOK. F. Reaktion mit dem Cer(IV)sulfat-Reagens: grau. Relative Retentionszeiten (t_R) von **2** in der HPLC., verglichen mit Peduncularin ($t_R = 1$): $t_R = 1{,}7$ mit Heptan/Äther/Methanol/25proz. Ammoniak 80:20:3:0,1 als Eluierungsmittel und $t_R = 0{,}95$ mit Chloroform/Methanol/25proz. Ammoniak 97:3:0,5.

3. *Physikalische Daten von Aristoserratin* (**2**). Smp. 199° (farblose Kristalle), $[\alpha]_D^{20} = +22{,}5°$ ($c = 1{,}9$, Chloroform). - UV.: 228 (4,42), 282 (3,82), 290 (3,75); min. 247 (3,41), 288 (3,75); Inflexion 275 (3,79). - CD. ($c = 0{,}014$, Äthanol): 208 (0), 227 (−9,7), 254 (−0,3), 278 (−2,9), 291 (0), 302 (+3,4). Zum Vergleich CD. von Aristotelin (**1**; $c = 0{,}014$, Äthanol): 208 (0), 229 (−10,3). - IR.: 3473 (HN), 3330 br. (HN), 2961, 2927, 1710 (C=O), 1469, 1456, 1388, 1307, 1294. - ^{1}H-NMR.: 8,18 (br. *s*, 1 H, H–N_a; verschwindet nach D_2O-Zugabe); 7,47 (*d*×*d*×*d*, $J = 7{,}5$, 1,5 und 0,8, 1 H, H–C(5)); 7,30 (*d*×*d*×*d*, $J = 7{,}5$, 1,5 und 0,8, 1 H, H–C(8)); 7,15 (*d*×*d*×*d*, $J = 7{,}5$, 6,5 und 1,5, 1 H, H–C(7)); 7,09 (*d*×*d*×*d*, $J = 7{,}5$, 6,5 und 1,5, 1 H, H–C(6)); 3,79 (*d*×*d*×*d*, $J = 5{,}7$, 2,5 und 1,5, 1 H, H–C(11)); 3,08 (*d*×*d*, $J = 16{,}8$ und 5,7, 1 H, H*exo*–C(10)); 2,80 (*d*×*d*, $J = 16{,}8$ und 1,5, 1 H, H*endo*–C(10)); 2,58 (*t*×*d*, $J = 13{,}8$ und 5,8, 1 H, H*endo*–

C(18)); 2,35 ($d\times d$, J=2,5 und 1,3, 1 H, H–C(16)); 2,18 ($d\times d\times d\times d$, J=14,2, 5,8, 2,5 und 2,0, 1 H, H*endo*–C(19)); 2,08 ($d\times d\times d$, J=3,8, 2,5 und 1,3, 1 H, H–C(14)); 1,92 ($d\times d\times d\times d$, J=14,2, 13,8, 5,6 und 3,8, 1 H, H*exo*–C(19)); 1,65 ($d\times d\times d$, J=13,8, 5,6 und 2,0, 1 H, H*exo*–C(18)); *ca.* 1,5 (br. *s*, 1 H, H–N_b; verschwindet nach D_2O-Zugabe); 1,38 und 1,19 (2 *s*, 3 H bzw. 6 H, 3 H–C(20), 3 H–C(21) und 3 H–C(22)). Entkopplungsexperimente: Einstrahlung bei 3,79→3,08 (*d*, J=16,8), 2,80 (*d*, J=16,8) und 2,35 (Verschärfung); 2,58→2,18 ($d\times d\times d$, J=14,2, 2,5 und 2,0), 1,92 ($d\times d\times d$, J=14,2, 5,6 und 3,8) und 1,65 ($d\times d$, J=5,6 und 2,0); 2,35→3,79 ($d\times d$, J=5,7 und 1,5) und 2,08 (Verschärfung); 1,65→2,58 ($d\times d$, J=13,8 und 5,8), 2,18 ($d\times d\times d$, J=14,2, 5,8 und 2,5) und 1,92 ($d\times d\times d$, J=14,2, 13,8 und 3,8). - ^{13}C-NMR.('off-resonance'): 216,6 (*s*, C(15)); 139,6 (*s*, C(2)); 135,8 (*s*, C(9)); 127,6 (*s*, C(4)); 121,5 (*d*, C(6)); 119,3 und 118,1 (2 *d*, C(5), C(7)); 110,6 (*d*, C(8)); 104,4 (*s*, C(3)); 58,5, 55,5 und 51,7 (3 *d*, C(11), C(14), C(16)); 57,4 (*s*, C(13)); 39,7 (*s*, C(17)); 35,2 (*t*, C(10)); 27,6 und 26,4 (2 *t*, C(18), C(19)); 27,6, 27,3 und 25,6 (3 *qa*, C(20), C(21), C(22)). - MS.: 308 (M^+, 67, $C_{20}H_{24}N_2O$), 293 (33, $C_{19}H_{21}N_2O$), 251 (11, $C_{17}H_{17}NO$), 236 (10, $C_{16}H_{14}NO$), 226 (18), 225 (100, $C_{15}H_{15}NO$), 194 (10, $C_{14}H_{12}N$), 184 (12, $C_{13}H_{14}N$), 183 (21), 182 (33, $C_{13}H_{12}N$), 181 (12, $C_{13}H_{11}N$), 180 (27, $C_{13}H_{10}N$ und $C_{11}H_{18}NO$, 2:1), 168 (17, $C_{12}H_{10}N$), 167 (21, $C_{12}H_9N$), 162 (13, $C_{10}H_{12}NO$), 154 (11, $C_{11}H_8N$), 143 (32, $C_{10}H_9N$), 130 (12, C_9H_8N), 110 (20), 84 (16), 69 (10), 58 (24), 55 (16); m^*: 308→251; 308→225. Zum Vergleich MS. von Aristotelin (1): 294 (M^+, 100, $C_{20}H_{26}N_2$), 280 (22), 279 (97, $C_{19}H_{23}N_2$), 238 (14), 237 (63, $C_{17}H_{19}N$), 223 (13), 222 (35, $C_{16}H_{16}N$), 212 (13), 211 (76, $C_{15}H_{17}N$), 195 (11), 194 (28, $C_{14}H_{12}N$), 183 (22, $C_{13}H_{13}N$), 182 (31, $C_{13}H_{12}N$), 181 (15, $C_{13}H_{11}N$), 180 (25, $C_{13}H_{10}N$), 168 (14, $C_{12}H_{10}N$), 167 (24, $C_{12}H_9N$), 157 (11, $C_{11}H_{11}N$), 144 (19, $C_{10}H_{10}N$), 143 (45, $C_{10}H_9N$), 132 (12, $C_9H_{10}N$), 130 (14, C_9H_8N), 120 (10, $C_8H_{10}N$), 117 (11, C_8H_7N), 108 (11, $C_7H_{10}N$), 70 (15), 58 (21).

4. *Reduktion von* **2** *mit* $NaBH_4$. Mit einem Überschuss an $NaBH_4$ wurden 13 mg (0,042 mmol) **2** in Methanol reduziert. Nach der üblichen Aufarbeitung wurden 11 mg eines (1:1)-Gemisches **3** erhalten. DC. (Chloroform/Methanol/25proz. Ammoniak 98:2:5, organische Phase): Rf(**2**) 0,75; Rf(**3**) 0,33 und 0,38. - MS. (Gemisch): 310 (M^+, 100), 295 (68), 277 (12), 253 (42), 236 (15), 228 (12), 227 (75), 220 (12), 209 (25), 194 (12), 184 (25), 183 (31), 182 (44), 181 (18), 180 (12), 170 (12), 169 (12), 167 (17), 156 (11), 155 (14), 144 (13), 143 (26), 130 (12), 122 (30), 85 (14), 73 (16), 70 (11), 58 (15), 57 (11).

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Tetrahedron Letters, Vol.22, No.34, pp 3275 - 3276, 1981
Printed in Great Britain

0040-4039/81/343275-02$02.00/0

ARISTOMAKINE, A NOVEL INDOLE ALKALOID FROM ARISTOTELIA SERRATA

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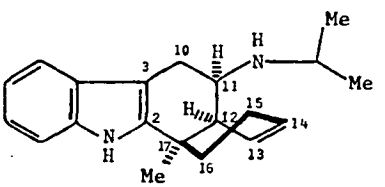
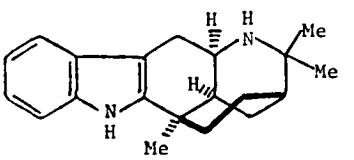
Abstract: The isolation and structural determination of aristomakine (I), an unusual indole alkaloid with an N-isopropyl group, is reported.

Indole alkaloids from Aristotelia spp.[1-10] are distinguished by the incorporation into their structures of a monoterpene unit which has not undergone previous rearrangement to loganin, although considerable subsequent rearrangement may take place. Aristomakine, $[\alpha]_D^{22}$ -79.1° (c 1.5 in $CHCl_3$), was isolated in 0.0008% yield from dried whole plant material of the New Zealand species A. serrata W.R.B. Oliver (Maori name: makomako). It is isomeric with aristoteline (II),[2,3] the major alkaloid of the plant, but n.m.r. spectroscopy showed it had one double bond, and hence one less ring than (II). From its u.v. spectrum, aristomakine has an indole nucleus, which as for (II) is substituted at C-2 and C-3 from the -ve Ehrlich test. This substitution is confirmed by the n.m.r. spectra; furthermore, the ^{13}C spectra of aristomakine and (II) show a close correspondence in resonance of their C-2 carbons (δ 136.3 and 135.9), suggesting that these carbons carry similar substituents: thus the only quaternary aliphatic carbon in aristomakine, which must bear the methyl group producing a 3-proton singlet at δ 1.36 in its ^1H n.m.r. spectrum, is presumably attached at C-2. This inference is supported by a series of strong ions between m/z 180 and 183 in the m.s. of both aristomakine and (II). The m/z 181 fragment from (II) has been formulated as (III)[3] and is considered to arise from the ion radical (IV).[3] The non-indolic nitrogen of aristomakine is secondary: it bears one proton exchangeable with D_2O, and the ^{13}C n.m.r. spectrum shows signals at δ 51.5 and 46.6 corresponding to two α methine carbons. Of the two protons which can be assigned to these methine groups, one produces a septet at δ 3.10 in the ^1H n.m.r. spectrum, and is coupled to two sets of geminal methyl protons; thus aristomakine has an N-isopropyl group. The other proton, resonating at δ 3.44, is coupled to two geminal protons which from their chemical shifts (δ 2.90 and 2.30) can be attributed to a methylene group attached to C-3 of the indole nucleus. These observations suggest a structure such as (I) with a skeleton of type (IV) for aristomakine. Structure (I) is supported by the m.s., in which the base peak appears at m/z 124 and is accompanied by a strong complementary ion at m/z 170. These ions may be formulated as (V) and (VI) and could arise by α-cleavage and retro-Diels-Alder fission of (I). Structure (I) has been confirmed by a series of decoupling experiments, which have established a sequence of protons attached to a chain of carbon atoms extending from C-10 to C-16. The protons in this sequence all show the expected chemical shifts, multiplicities, and coupling constants corresponding in structure and relative stereochemistry to (I).

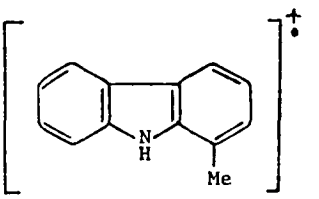
It seems likely that aristomakine, with its unusual N-isopropyl group, is formed biosynthetically by cleavage of the piperidine ring of (II), with retention of configuration at the chiral centres 11, 12 and 17.



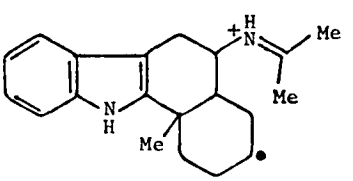
(I), Aristomakine



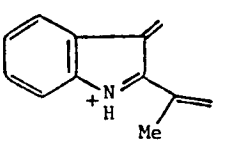
(II), Aristoteline



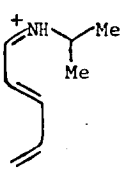
(III), m/z 181



(IV), m/z 294



(VI), m/z 170



(V), m/z 124

Acknowledgments- We thank the Australian Research Grants Committee for financial support, the National NMR Centre, Canberra, for spectra, the Australian Development Assistance Bureau for an Australian Commonwealth Scholarship (to M.A.H.), and the New Zealand Forestry Service for supply of plant material.

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(Received in UK 3 June 1981)

MAKOMAKINE AND MAKONINE, NEW INDOLE ALKALOIDS FROM ARISTOTELIA SERRATA

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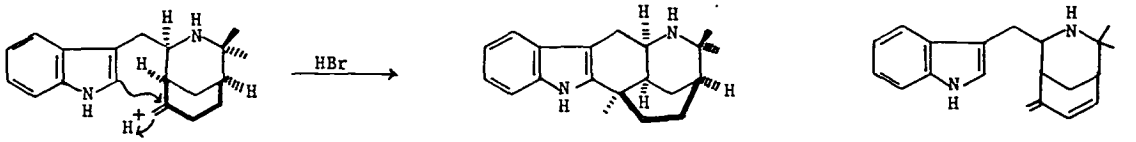
Abstract — A key intermediate, makomakine (I), involved in the proposed scheme of biosynthesis[10] of the Aristotelia alkaloids, has been isolated from an A. serrata extract, together with makonine (II), a dehydro-aristotelinone.

A number of novel indole alkaloids occur in the New Zealand elaeocarpaceous plant Aristotelia serrata W.R.B. Oliver (Maori name: makomako),[1,2,3] and in other Aristotelia spp.[4,5,6,7,8,9] A possible mode of biogenesis of these alkaloids has been put forward[10] involving the hypothetical key intermediate (I). We report the isolation in small amount of a base, m.p. 99-100°, $[\alpha]_D^{19}$ (+) 131.2° (c 0.5, $CHCl_3$), from A. serrata whose structure is shown to correspond with (I). This base, for which the name makomakine is suggested, has an indole nucleus from its U.V. spectrum; its ^1H and ^{13}C n.m.r. spectra show that it has one double bond in a vinylidine group, and from its molecular formula $C_{20}H_{26}N_2$ it must thus have two ring systems in addition to the indole nucleus. Makomakine gives a positive Ehrlich test, and a singlet at δ6.95 in its ^1H n.m.r. spectrum indicates that the 2-position of the indole is unsubstituted. On the other hand, the 3-position evidently bears a methylene group from the strong m/z 130 peak in its m.s.,[11] and from the geminally-coupled pair of protons at δ2.75 and 2.70 in its ^1H n.m.r. spectrum. These are further coupled to a methine proton, which from its chemical shift (δ3.48) is adjacent to N. The non-aromatic nitrogen is secondary: it bears a proton exchangeable with D_2O. Thus far, the structure resembles that of sorelline (III), isolated from A. peduncularis;[6] like the latter base, makomakine has a pair of geminal methyl groups, but it differs from sorelline in having two more hydrogens and one less olefinic group. The tentative structure (I) for makomakine suggested by these data is supported by m.s. and by its ^1H and ^{13}C n.m.r. spectra; the chemical shifts, multiplicities and coupling constants of the aliphatic and olefinic protons are in accord with (I), and the structure was confirmed by a conversion to aristoteline (IV),[1] whose structure and absolute stereochemistry are known from X-ray crystallography. When makomakine (I) was treated at room temperature with 47% hydrobromic acid, it gave crystalline (IV) in 10% yield, identical with the natural alkaloid. This experiment, which fixes at the same time the absolute configuration of

makomakine, supports the suggestion[10] that (I) is a biogenetic precursor of (IV) and of other Aristotelia alkaloids.

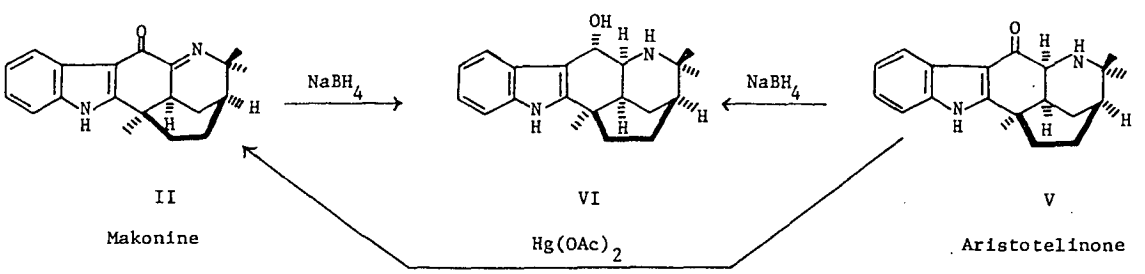


I
Makomakine

IV
Aristoteline

III
Sorelline

Another minor alkaloid, named makonine, was isolated from the same extract as hexagonal crystals, m.p. 310-312° (d), $[\alpha]_D^{19}$ (+) 431.1° (c 0.93, MeOH + $CHCl_3$). Like aristoteline (IV), it gave a negative Ehrlich test, and its n.m.r. spectra showed the presence of a pair of geminal dimethyl groups, plus an extra methyl attached to a quaternary carbon. However, it contained a carbonyl group, and the non-indolic nitrogen appeared to be tertiary. The u.v., i.r. ^1H and ^{13}C n.m.r. spectra were broadly similar to those of aristotelinone[2] (V), which has a carbonyl group conjugated with the indole nucleus, but makonine has two less hydrogens than (V), and an extra olefinic carbon. Structure (II) suggested by these data was confirmed by conversion of aristotelinone into makonine in 25% yield by mercuric acetate oxidation; furthermore, both (II) and (V) on borohydride reduction gave as major product the same secondary alcohol (VI).[2]



II
Makonine

VI

V
Aristotelinone

We thank the Australian Research Grants Committee for financial support, the National NMR Centre for spectra, and the Australian Development Assistance Bureau for an Australian Commonwealth Scholarship (to M.A.H.).

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Received, 11th April, 1981

HETEROCYCLES, Vol.12, No.12, 1979

BIOGENESIS OF ARISTOTELIA ALKALOIDS

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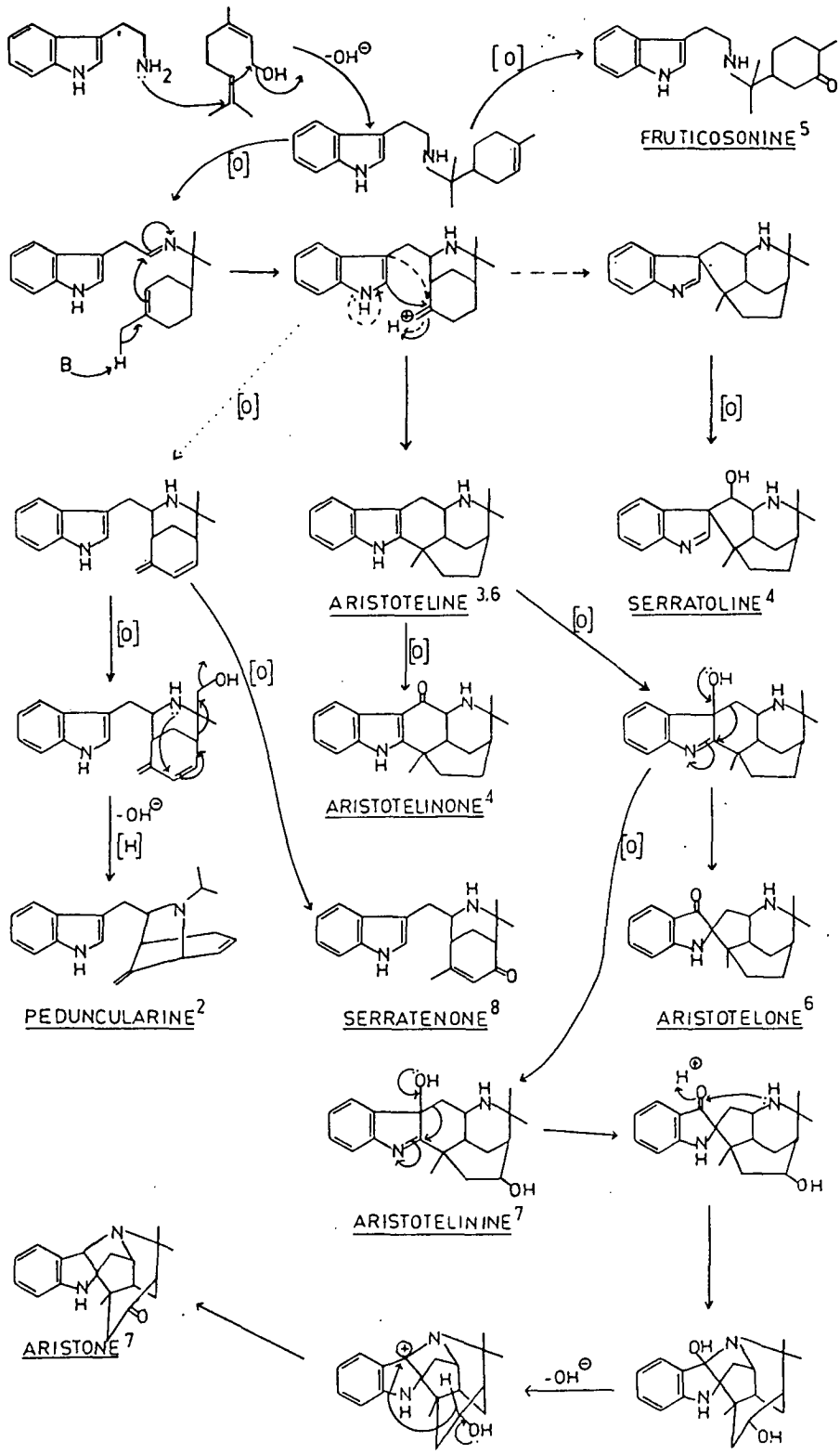
Abstract A possible biosynthetic scheme for the Aristotelia alkaloids is presented.

The Aristotelia spp. belong to the family Elaeocarpaceae and occur in countries bordering the South Pacific: A. peduncularis[1,2] is endemic in Tasmania, A. serrata[3,4] and A. fruticosa[5] in New Zealand, and A. chilensis[6,7] in South America. About twenty-five alkaloids have so far been isolated[1-8] from these plants, some of unknown or incompletely known structures.

Apart from the Aristotelias, of which there are one or two other species less well defined botanically, certain Elaeocarpus spp. from New Guinea belonging to the same family contain a range of indolizidine and related alkaloids[9], including one with an indole residue. The alkaloids so far reported from the Aristotelias all have 20 carbon atoms and two nitrogens, and contain an indole or some closely related nucleus; furthermore, they all have geminal dimethyls, plus an extra methyl group except one example which has a vinylidine group instead: these features strongly suggest that the Aristotelia alkaloids originate in a tryptamine and a monoterpenoid unit. A large range of well-known indole alkaloids have a similar origin, starting ultimately from geraniol as the terpenoid unit, but this undergoes profound structural changes to secologanin before being linked to the tryptamine[10].

The Aristotelia alkaloids on the other hand appear to owe their origin to a linkage between tryptamine and an unarranged terpenoid unit such as geraniol, followed by a variety of molecular rearrangements as in the biosynthesis of other indole alkaloids[10]. The following scheme, which at present lacks experimental support but may serve as a working hypothesis for labelling experiments, suggests a possible biogenetic pathway for all the Aristotelia alkaloids so far reported. The transformations involved in the scheme, such as oxidation at an α-position to nitrogen, or formation of a new N-C bond through nucleophilic attack by a nitrogen, are well-known and all have analogies in alkaloid biogenesis. The scheme presents a feasible pathway to peduncularine[1,2], which is unique amongst naturally-occurring alkaloids in having an N-isopropyl group. The plausible route from aristoteline to the A. chilensis alkaloids aristotelinine, aristotelone and aristone, was proposed by Bittner et al.[7]


FRUTICOSONINE 5
ARISTOTELINE 3,6
SERRATOLINE 4
ARISTOTELINONE 4
PEDUNCULARINE 2
SERRATENONE 8
ARISTOTELONE 6
ARISTOTELININE 7
ARISTONE 7

We thank the Australian Research Grants Committee for financial support, and the Australian Development Assistance Bureau for an Australian Commonwealth Scholarship (to M.A.H.).

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Received, 13th August, 1979